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Aspectos clínicos del tratamiento de por wine stains con luz intensa pulsada
Clinical aspects of the intense pulsed light treatment of port wine stains

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ABSTRACT

1. Introduction

Vascular lesions are a heterogeneous group of anomalies which differ in both their clinical presentation and histopathological features. The adequate diagnosis is of paramount importance because of their distinct differences in morbidity, prognosis, and treatment.

Cutaneous vascular malformations, comprising a significant part of the vascular lesions, are rare disorders that occur in approximately 0.3% to 0.5% of the population. These lesions are often confused with the common vascular birthmark-infantile hemangioma, although they are much less frequently seen.

By the use of confusing terminology and classifications, the identification of vascular anomalies was historically hampered. For a long period of time, the use of an inaccurate nomenclature has led to confusion. In 1863 Virchow and Wagner in their early published classification characterized vascular lesions according to the vessel's pathologic appearance. Vascular growths were divided into angiomas and lymphangiomas.

A main step along the difficult path to clarity was the publication of Mulliken and Glowacki in 1982, in which vascular birthmarks were divided into two major categories: hemangiomas and malformations. Hemangiomas were differentiated from vascular malformations by their clinical appearance, histopathologic features and biologic behavior.

Otherwise Mulliken's biologic classification has been widely adopted by clinicians to differentiate vascular birthmarks and is the accepted classification of the International Society for the Study of Vascular Anomalies (ISSVA). Consequently, the updated ISSVA/biologic classification divides vascular birthmarks into vascular tumors and vascular malformations. This classification is useful for managing patients and provides a framework for study of these lesions.

Capillary malformations (CMs) include port wine stains (PWS) and telangiectasias. These

slow-flow vascular anomalies occur in approximately 3 of 1000 infants and have an equal sex distribution. Port wine stains are usually noted at birth and are believed to represent an error in vascular development occurring during embryogenesis. They may be single or multiple lesions and present as small patches or involve an entire limb or portion of the face. The clinical behavior of port wine stains varies according to their anatomic location.

They usually represent an isolated condition, but some of them could be associated with serious syndromes that must be recognized in a timely fashion. These include Sturge-Weber syndrome, Klippel-Trenaunay syndrome, and other less common constellations of findings.

PWS are diagnosed on the basis of their clinical appearance. Once the diagnosis of PWS is established, the patient should be carefully examined for the presence of underlying vascular malformations and associated congenital anomalies.

PWS were considered to be essentially untreatable until the advent of argon laser. Other treatments have included Bucky (=Grentz) ray, sclerosing agents, cauterization, cryotherapy, carbon dioxide snow, liquid nitrogen, cortisone, protamine, heparin locally and systemically, obliteration by ligature of vessels, ultraviolet and infrared radiation and dermabrasion. All these techniques usually have replaced the PWS with scarring and pigment changes. Another attempt to treat port wine stain is surgery by rotation of flaps, excision and skin grafting, but it has been difficult to achieve a natural texture and color of the skin.

Nowadays the standard treatment for PWS is the therapy with light devices. Treatment with light devices is well tolerated and the rate of persistent side-effects is rather low. Nevertheless realistic information prior to treatment is extremely important. Patients should never be promised any type of success or least of all a total clearance of PWS. Many factors, such as size, color, localization, hypertrophy, or vessel architecture, are supposed to influence the results of the treatment. Among the various light devices used for treating PWS, pulsed dye laser (PDL) is believed to have the best efficacy and safety profile and is often considered a “gold standard of treatment”. Other machines that are widely available are Nd:YAG laser, KTP laser and intense pulsed light (IPL).

IPL devices emit polychromatic incoherent high-intensity pulsed light with an emission spectrum ranging from 400 to 1400 nm and pulse durations in the millisecond range. Theoretically, IPL systems have a potential advantage over laser systems because they incorporate the highly oxyhemoglobin selective wavelengths around 577 to 600 nm and also emit longer wavelengths allowing deeper penetration into the dermis and deeper capillary destruction.

Thus it is of great interest to assess the clinical aspects of the treatment of PWS using an IPL with broadband irradiation and long pulse durations.

2. Hypotesis and Objectives

On the base of the previously known data and considering the most contemporary knowledge of anatomy and pathophysiology of the port wine stains and the possibilities of the light devices for treatment of vascular lesions, we aimed to investigate the abilities of intense pulse light in the clinical treatment of port wine stains.

We established the following hypothesis:

1. The intense pulsed light treatment could be the first line treatment of port wine stains because of its high efficacy and safety profile.
2. The clinical results of intense pulsed light treatment of port wine stains are related with the anatomical location, color and size of the lesions and patients' age.
3. The recurrence rate after successful treatment of port wine stains with intense pulsed light depends on patients' age at the beginning of the treatment course.

In order to test the hypothesis we set the following objectives:

1. To review and describe the intense pulsed light procedures in treatment of port wine stains during the last seven years.

2. To evaluate the efficacy (clearance rate) of intense pulsed light treatment of port wine stains according to the characteristics of the lesions (anatomical location, color and size) and the age of the patients.

3. To check if there is any relation between the recurrence rate of the port wine stains treated with intense pulsed light and the age of the patients at the beginning of the treatment course.

3. Materials and Methods

In this work a retrospective descriptive study was conducted based on the revision of the clinical data and photo documentation of the patients with vascular anomalies treated with different light devices. The patients were treated between November 2008 and July 2015 at the Department of Dermatology of Military Medical Academy in Sofia, Bulgaria. All the treatments were performed by the same clinical team with the main investigator of the present study being the head of the team. A minimal follow-up of 12 months after the last procedure was selected for the design of the study.

A total of 149 patients with PWS with different anatomical locations treated with IPL were explored for their possible inclusion in the study. As an exclusion criteria were selected any previous treatments and uncompleted follow-up. Thus a total of 144 patients were included. Of them, 68 (47.2%) were male and 76 (52.8%) female. The age of the patients at the time of the first treatment varied from 8 months to 47 years (mean age 31.4 years).

We divided the patients in three different groups according to the color and texture of the lesions: pink, red and thickening. Another important issue of practical point of view was the location of the lesions on the body area. Considering that we also divided the patients into three groups: with affection of the head, affection of the neck and affection of the trunk and extremities.

The treatment process and the survey were approved by the institutional ethics committee. All patients signed an informed consent form before the first procedure. For the patients under age of 18 the consent was signed by their parents.

Photo documentation was performed with Canon Powershot G3X digital camera prior to each single treatment, at 1 month, at 6 months and finally at 12 months after the last procedure.

All patients' data such as demographics, skin type, characteristics of PWS including color and location, treatment parameters, percentage of clearing and treatment complications were recorded and entered into a database specially designed for this survey.

The patients in our study were all treated using the Lux G handpiece- a novel intense pulsed light system which delivers dual-band spectral output in the 500 nm to 670 nm region and in the 870 nm to 1400 nm region. The spot size of the handpiece is 15×10 mm and the maximum fluence is 70 J/cm^2. The treatment intervals were 4 to 6 weeks for 3 to 6 treatments sessions.

Treatment efficacy was evaluated according to the photographic analysis. Each pre- and postoperative photograph was subjected to evaluation by computerized, triple objective comparative assessment of color shading with use of the program Skin Lesion Color Change (SLCC) created by Pawel Szychta.

Patient responses were divided into four groups according to the clearance rate of the lesion: excellent- 75-100% clearing; good- 50-75% clearing; fair- 25-50% clearing; poor- less than 25% clearing.

The response rate was determined via the following formula:

(cases of excellent + cases of good + cases of fair) / total cases

Clinical effect was evaluated with photographs 6 and 12 months after the last treatment and data were analyzed using the chi-squared test or Fisher's exact probability.

4. Results

There were 76 (52.8%) females and 68 (47.2%) males among our 144 patients. Seventy five were children under 18 years old and 69 were adults older than 18 years. In the group of children there were 33 females and 42 males and in the group of adults there were 43 females and 26 males. Sixty seven patients (47%) had Fitzpatrick skin type III, 48 (33%) patients had Fitzpatrick skin type IV and 29 (20%) patients with skin type II

To examine the relation between PWS size and the treatment efficacy, the patients were placed into 3 groups according to the size of their PWS: (i) less than 20 cm^2 where we have found 92 patients (67%), (ii) 20-40 cm^2 with 35 patients in the group (24%) and (iii) 40 cm^2 or more where 17 patients (12%) were found.

Fisher's Exact Test was applied and analysis showed a significant statistical association ($p<0,001$) between clearance rate and the size of the treated port wine stain. Lesions less than 20 cm^2 had the best response to IPL. In this group 23 (25%) of 92 lesions had more than 75% clearance rate; this result was not seen in the other two groups. When decreases the clearance rate, this trend is reversed, highest frequency has the group of lesions with size 40 cm^2 or over. For lesions with size 20-40 cm^2, the biggest group of 20 (57.1%) PWSs were with clearance rate between 25%-50%. In the group of patients with lesions bigger than 40 cm2, there were not even one patient with clearance rate more than 50%. Seven (41.2%) of these patients had less than 25% clearance. When a lesion was very large (40 cm^2 or more), the mean decrease in size was initially poor, but response to subsequent treatments was steady.

In our survey we examined whether the age of treated patients affected their response to IPL procedures. There were 69 (47.92%) adults and 75 (52.08%) children in the study. We found that there was statistically significant association between the age of the patients and the clearance rate after IPL treatments.

At the statistical analysis of results, we could observe that in children group (younger than 18 years) the clearance rate was bigger compared to the adults. A clearance rate more than 75% in the youngest group (younger than 1 year) was seen in 58.3% (7/12) of patients, whereas in the adult group (older than 18 years) it only was 8.7% (6/69). Clearance rate from 50% to 75% was highest in the group of children from 1 to 6 years: 43.9% (18/41). Half of the patients (11/22) at ages between 6 to 18 years had a clearance rate more than 50%. In the group of adults (older than 18years) 63.8% (44/69) of them had 25%-50% lightening.

In the present study we also evaluated the association between the number of treatments needed to achieve maximum clearance rate and the age of the patients. The patients were divided into three groups: (i) less than 5 treatments, (ii) from 5 to 10 treatments and (iii) more than 10 treatments. Fisher's Exact Test was applied and it was found statistical significance ($p<0.001$) between the number of treatments and the age in the group of children younger than 1 year and in the group of adults.

75% (9/12) of children under the age of 1 needed 5 or less treatments to achieve best results (more than 75% lightening) and none of them needed more than 10 treatments. On the other hand, in the group of adults 1.4% (1/69) needed 5 or less procedures and 72.5% (50/69) needed more than 10 procedures.

One hundred forty-four patients in our study were divided into three types according to their clinical manifestation: (i) 57 pink (39.58%); (ii) 69 red (47.92%); and (iii) 18 thickening (12.50%). In the group of pink lesions 89% (51/57) of patients were younger than 18 years and 11% (6/57) were older than 18 years. Sixty five percent (45/69) of patients with red lesions were adults and 35% (24/69) were children. There were no children in the group with thickening lesions.

In our study we tried to find where there is an association between the color of the lesion and the clearance rate. Statistical significance (Fisher's Exact Test, $p<0.001$) was found among the types.

The clearance rate more than 75% was highest in the group of patients with pink lesions- 22.8% (13/57), followed by the patients with red lesions-14.5%. There were no patients with this clearance rate in the last group with thickening lesions. More than 50% reduction of the lesion was achieved in the patients group with pink lesions- 40.4% (23/57) and red- 21.7% (15/69) lesions. These patients had been accepted as good responders to IPL treatments. In the group of thickening lesions there were no PWS who responded well (more than 50% clearing) to treatments. In this group 44.4% (8/18) of lesions achieved suboptimal result with a clearance rate less than 25%.

We evaluated the relationship between the PWS location (head, neck and extremities) and the treatment efficacy. Fisher's Exact Test was applied and showed a significant statistical association ($p<0.001$) between two of the indicators.

Of head lesions 24.2% (23/95) had the greatest mean improvement (more than 75% clearing rate) contrary to the neck and extremities lesions where there were no patients with that high percentage of improvement. In the group of PWSs with neck location, 46.4% (13/28) had a clearance rate between 50% to 75% and 53.6% (15/28) had a clearance rate from 25% to 50%. There were no neck lesions with more than 75% clearance so as no lesions with clearing less than 25%. Approximately 57.1% (12/21) of the extremities lesions had about 25% to 50% clearance and 38.1% (8/21) had less than 25% clearance. In this group there were only 4.8% (1/21) PWS with a clearance rate between 50%-75% which was the highest rate achieved.

After we found out that lesions with head location had best response to IPL treatments, we examined whether different parts of the head had variations in clearance rate. We separated the head in four zones: (i) forehead, (ii) peripheral face, (iii) central face and (iiii) mixed.

Our results showed that lesions over the forehead showed the best response to IPL treatments. In this group 92.9% (13/14) of PWSs had the highest clearance rate (more than 75%). Peripheral facial lesions had good response: 56.1% (23/41) of them were with clearing between 50%-75% and there were none lesions with less than 25% clearance. In the group of central PWSs clearance was less than the previous two groups: 67.9% (19/28) of lesions had clearance rate 25%-50% and 25% (7/28) of them had a clearance rate less than 25%.

During our research we realized that location of the PWS seemed to be somehow related to the required energy that we applied and the number of treatments. We used Chi-Square Test to evaluate it statistically and found that there was a significant association between the location of the lesion and the employed setting and the number of treatments.

We found that lesions located on the extremities needed higher energy (more than 50J) and higher number of treatments (more than 10). In the group of neck lesions almost 64.3% (18/28) needed the lowest energy between 30J to 40J. PWSs in head location needed the less number of procedures: 40% (38/95) of them needed 5 or less procedures.

Having in mind that some PWSs can recur years after treatment, despite a promising response to initial treatments, every patient who finished his procedures was asked to come on a follow up visit once every year. During the follow up visits of our patients we noted that some of PWSs had become darker compared to the results at the end of their treatment sessions.

We established that 28.47% (41/144) of all patients had recurrence, 1 year to 3 years after the end of their treatments. Seven (17.1%) patient's lesions had become redder 1 to 2

years after the IPL treatments. Thirteen (31.7%) patients had recurrence between 2 and 3 years after the treatments and 21 (51.2%) patients after more than 3 years. We noted that it was only focally and a new IPL treatment showed significant improvement.

In our survey we found that only 1 of 12 patients (8.33%) under one year had recurrence after the end of his treatment. In the group of children between 1 to 6 years only 5 of 41 (12.20%) had their lesions darker. Six of 22 (27.27%) children from the age of 6 to 18 had recurrence. Contrary to the children's groups, the recurrence rate in the group of adults (older than 18 years) was much higher: 29 of 69 patients (42.03%).

We used Chi-Square Test to demonstrate whether there was statistical significant ($p<0,001$) association between the color of the PWSs and their recurrence. It was clearly seen that only 7% (4/57) of pink lesions had recurrence, compared to 30.4% (21/69) of red and 88.9% (16/18) of thickening purple lesions.

5. Conclusions

1. Intense pulsed light is a highly effective approach for treatment of port wine stains presenting different anatomical locations in patients with distinct ages and skin types.

2. Port wine stains with smaller size (less than 20 cm^2) have better response to IPL treatment than larger ones, irrespectively of patient's age.

3. The clearance rate after intense pulsed light treatment of port wine stains decreases as patient's age increases.

4. The number of treatment sessions with intense pulsed light increases with the increase of the patient's age.

5. The response rate of port wine stains to intense pulsed light differs according to their anatomical location: the lesions on the head have better response com-

pared to those in non-facial localization, being the forehead lesions the ones with best response compared to the lesions on the central and peripheral facial areas.

6. The recurrence rate of port wine stains treated with intense pulsed light gets higher as the color of the lesions gets darker and the patient's age increases. Patients with lighter lesions and younger age tend to have lower recurrence rate.

RESUMEN

1. Introducción

Las lesiones vasculares son un grupo heterogéneo de anomalías que difieren tanto en su presentación clínica como en sus características histopatológicas. Por esta razón un diagnóstico adecuado y correcto es de gran importancia debido a la heterogéneo que estas lesiones presentan en cuanto a morbilidad, pronóstico y tratamiento.

Las malformaciones vasculares cutáneas comprenden una parte significativa de las lesiones vasculares y están consideradas como enfermedades raras que afectan entre el 0,3% y el 0,5% de la población. Estas lesiones se confunden a menudo con la lesión vascular congénita más común, el hemangioma infantil, aunque son mucho menos frecuentes.

Por otro lado, la identificación de las anomalías vasculares ha sido históricamente un tanto compleja y durante años el uso de nomenclaturas inexactas ha generado mucha confusión. En el año 1863 Virchow y Wagner caracterizaron las lesiones vasculares en base al aspecto patológico de los vasos. De esta manera, los crecimientos vasculares anómalos fueron divididos en dos grupos: angiomas y linfangiomas.

Un paso importante en el difícil camino hacia la clarificación en la definición de estas lesiones fue dado por Mulliken y Glowacki en 1982, gracias una publicación en la que dividieron en dos categorías principales las marcas vasculares de nacimiento: hemangiomas y malformaciones vasculares. Los hemangiomas fueron diferenciados de las malformaciones vasculares por su apariencia clínica, sus características histopatológicas y por el comportamiento biológico.

Por otro lado, la clasificación biológica de Mulliken está aceptada ampliamente por los especialistas en la materia, con el fin de diferenciar las manchas vasculares congénitas y actualmente es la clasificación adoptada por la Sociedad Internacional para el Estu-

dio de las Anomalías Vasculares (ISSVA). En la práctica clínica, la clasificación actualizada de la ISSVA divide las manchas vasculares congénitas en tumores vasculares y en malformaciones vasculares. Esta clasificación resulta útil para la clasificación de los pacientes y proporciona un marco clínico idóneo para la investigación de estas lesiones.

Las malformaciones capilares incluyen las definidas como Port Wine Stains (PWS o manchas rojo-vinosas) y las telangiectasias. Estas anomalías vasculares de flujo lento aparecen aproximadamente en 3 de cada 1000 nacidos y tienen igual distribución por sexo. Las PWS están presentes desde el nacimiento y se cree que se deben a un fallo en el desarrollo vascular que se produce durante la embriogénesis. Pueden ser lesiones solitarias o múltiples y se presentan como pequeñas manchas o bien pueden ocupar un miembro entero o parte de la cara. El comportamiento clínico de las PWS varía según su localización anatómica.

Las PWS por lo general se presentan como una entidad aislada, pero en algunos casos podrían estar asociadas con síndromes graves que no han de pasar desapercibidos. Estos incluyen el síndrome de Sturge-Weber o el síndrome de Klippel-Trenaunay entre otros. Por tanto las PWS se diagnostican por su manifestación clínica, pero una vez establecido el diagnóstico, el paciente debe ser examinado cuidadosamente para detectar la presencia de malformaciones vasculares subyacentes y posibles anomalías congénitas asociadas.

Las PWS se consideraban inicialmente intratables hasta la aparición del láser de argón. No obstante otros tratamientos han sido utilizados para tratar estas lesiones, como el rayo Bucky (= Grentz), los agentes esclerosantes, la cauterización, la crioterapia, el dióxido de carbono, el nitrógeno líquido, la corticoterapia, la protamina, la heparina local y/o sistémica, la obliteración por ligadura de los vasos, la radiación ultravioleta e infrarroja y la dermoabrasión. Todas estas técnicas por lo general han mostrado ser útiles para tratar las PWS al producir cambios en la cicatrización y en

la pigmentación. Otra alternativa para tratar las PWS es la cirugía exerética y la reparación con colgajos de rotación o con injertos de piel, aunque a veces resulta difícil lograr una textura y un color natural de la piel.

En la actualidad el tratamiento más comúnmente aceptado de las PWS es la terapia con dispositivos de luz. El tratamiento con estos dispositivos es bien tolerado y la tasa de efectos secundarios es más bien baja. No obstante, una información amplia y realista sobre las posibilidades de éxito antes del tratamiento es extremadamente importante y el paciente tiene que entender las espectativas. A los pacientes nunca se les puede asegurar la desaparición total de las PWS después del tratamiento. Varios factores como el tamaño, el color, la localización, la hipertrofia o la arquitectura vascular, influyen significativamente en los resultados del tratamiento.

Entre los diversos dispositivos de luz utilizados para tratamiento de las PWS, se cree que el láser de colorante pulsado (PDL) posee el mejor perfil de eficacia y seguridad y es a menudo considerado como el "*gold standar*" en el tratamiento de estas lesiones. Otros dispositivos disponibles en este sentido son el Nd: YAG, el láser de KTP y la luz intensa pulsada (IPL).

Los dispositivos IPL emiten luz pulsada de alta intensidad policromática con un espectro de emisión que puede variar desde 400 a 1400 nm y con una duración del pulso en el rango de milisegundos. Teóricamente, los sistemas IPL tienen una ventaja potencial sobre los sistemas láser porque incorporan las longitudes de onda alrededor de 577 a 600 nm, a las que la oxihemoglobina es altamente selectiva y también emiten longitudes de onda más largas que permiten una penetración más profunda en la dermis y una destrucción capilar más amplia.

Por tanto, resulta de gran interés evaluar los aspectos clínicos del tratamiento de las PWS utilizando el sistema de IPL con irradiación de una banda ancha y duración larga del pulso.

2. Hipótesis y objetivos

En base a los conocimientos más actualizados sobre la anatomía y la fisiopatología de las PWS y las posibilidades de los dispositivos de luz en el tratamiento de lesiones vasculares, nos planteamos investigar las capacidades de la luz intensa pulsada (IPL) para tratamiento clínico de las PWS.

Las hipótesis de planteadas en el estudio fueron las siguientes:

1. La luz intensa pulsada podría ser la primera opción de tratamiento de las PWS por tener una eficacia y un perfil de seguridad altos.
2. Los resultados clínicos del tratamiento de las PWS con IPL estarían relacionados con la localización anatómica, el color y el tamaño de las lesiones y la edad de los pacientes.
3. La tasa de recurrencia después un tratamiento con éxito de las PWS con IPL dependería de la edad de los pacientes al inicio del curso de tratamiento.

Para comprobar las hipótesis se plantean los siguientes objetivos:

1. Analizar y describir los procedimientos de tratamiento de las PWS con IPL efectuados en los últimos siete años.
2. Evaluar la eficacia (tasa de desaparición) del tratamiento de las PWS con IPL en función de las características de las lesiones (localización anatómica, color y tamaño) y la edad de los pacientes.
3. Comprobar si existe alguna relación entre la tasa de recurrencia de las PWS tratadas con IPL y la edad de los pacientes al inicio del curso de tratamiento.

3. Materiales y métodos

Este trabajo está basado en un estudio retrospectivo descriptivo de los datos clínicos y la documentación fotográfica disponible de pacientes con anomalías vasculares trata-

dos con diferentes dispositivos de luz en un mismo centro, por parte del mismo equipo médico. Los pacientes fueron tratados entre noviembre de 2008 y julio de 2015 en el Departamento de Dermatología de la Academia Médica Militar en Sofía, Bulgaria. Todos los tratamientos fueron se realizados por el mismo cuadro médico siendo el investigador principal del presente estudio la responsable principal del equipo. Los pacientes del estudio tuvieron un seguimiento mínimo de 12 meses después del último procedimiento operatorio con luz pulsada.

Un total de 149 pacientes con PWS en diferentes localizaciones anatómicas y que fueron tratados con IPL fueron considerados candidatos para la inclusión en el estudio. Como criterios de exclusión se consideraron aquellos tratamientos previos de cualquier naturaleza y un seguimiento incompleto de los pacientes. Es por ello que finalmente un total de 144 pacientes fueron incluidos. De ellos 68 (47,2%) fueron hombres y 76 (52,8%) mujeres. La edad de los pacientes en el momento del primer tratamiento oscilaba desde los 8 meses de edad a 47 años (edad media 31,4 años).

Se crearon tres grupos de pacientes en función del color de las lesiones: pacientes con lesiones de color rosa, pacientes con lesiones de color rojo y pacientes con lesiones con engrosamiento cutáneo. Otro aspecto importante desde el punto de vista práctico fue la localización de las lesiones en la zona del cuerpo. En base a esta premisa, dividimos a los pacientes en tres grupos: pacientes con afectación de la cabeza, pacientes con afectación del cuello y pacientes con afectación del tronco y las extremidades.

Tanto el protocolo de tratamiento como el estudio fueron aprobados por el comité de ética de la institución hospitalaria donde se realizó el trabajo. Todos los pacientes firmaron un consentimiento informado antes del primer procedimiento. En los casos de los pacientes menores de 18 años de edad, el consentimiento informado fue firmado por sus padres.

La documentación fotográfica se llevó a cabo con una cámara digital Canon Powershot G3X antes de cada tratamiento individual, al mes, a los seis meses y a los 12 meses después del último procedimiento.

Todos los datos de los pacientes, tales como los demográficos, el tipo de piel, las características de las PWS incluyendo el color y la ubicación, los parámetros del tratamiento, la tasa de desaparición, y las complicaciones del tratamiento fueron registradas y se introdujeron en una base de datos especialmente diseñada para el estudio.

Todos los pacientes fueron tratados mediante la pieza de mano Lux G- un sistema de luz intensa pulsada novedoso que ofrece una banda espectral doble en la región de 500 nm a 670 nm y en la región de 870 nm a 1400 nm. El tamaño del punto de la pieza de mano es de 15 × 10 mm y la fluencia máxima es de 70 J / cm2. Los intervalos durante el curso de tratamiento fueron de 4 a 6 semanas y se efectuaron entre tres y seis sesiones en función de los resultados que se fueron obteniendo.

La eficacia del tratamiento fue evaluada en la base de análisis fotográfico. Las fotografías pre y postoperatorias fueron evaluadas con un programa informático, con comparación triple objetiva del color, Skin Lesion Color Change (SLCC) creado por Pawel Szychta.

De tal forma se realizaron cuatro grupos de pacientes dependiendo de la tasa de desaparición de las lesiones. Excelente: 75-100% de desaparición; muy bueno: 50-75% de desaparición; bueno: 25-50% de desaparición; regular: menos de 25% de desaparición. La tasa de respuesta al tratamiento fue determinada mediante la siguiente fórmula:

(casos excelentes + casos muy buenos + casos buenos) / número *total de los casos*

El efecto clínico fue evaluado mediante las fotografías a los 6 y a los 12 meses después del último tratamiento y los datos se analizaron mediante la prueba de chi-cuadrado o probabilidad exacta de Fisher.

4. Resultados

Los resultados clínicos obtenidos en 144 pacientes con PWS tratados con IPL fueron analizados. De ellos 76 (52,8%) fueron mujeres y 68 (47,2%) varones. Setenta y cinco fueron menores de 18 años, 69 fueron adultos mayores de 18 años. En el grupo de niños hubo 33 de sexo femenino y 42 de sexo masculino; en el grupo de los adultos se trataron 43 mujeres y 26 varones. Sesenta y siete pacientes (47%) tuvieron fototipo de piel Fitzpatrick III, 48 (33%) pacientes- Fitzpatrick IV y 29 (20%) pacientes- Fitzpatrick II.

Para examinar la relación entre el tamaño de las PWS y la eficacia del tratamiento se realizaron tres grupos de pacientes en base al tamaño de las PWS: (i) grupo de lesiones de menos de 20 cm^2 en el que encontramos 92 pacientes (67%), (ii) grupo de lesiones de 20 a 40 cm^2 con 35 pacientes (24%) y (iii) grupo de lesiones de 40 cm^2 o más, donde encontramos 17 pacientes (12%).

La prueba exacta de Fisher se aplicó para el estudio analítico y éste mostró una asociación estadísticamente significativa ($p < 0,001$) entre la tasa de desaparición y el tamaño de las PWS. Las lesiones de menos de 20 cm^2 tuvieron la mejor respuesta a la ILP. En este grupo 23 (25%) de 92 lesiones tuvieron una tasa de desaparición de más de 75% y este resultado no fue observado en los otros dos grupos.

Para lesiones con tamaño de 20-40 cm^2, 20 pacientes (57,1%) tuvieron una tasa de desaparición entre el 25% y el 50%. En el grupo de los pacientes con lesiones superiores de 40 cm^2, no hubo casos cuya tasa de desaparición fuera de más de 50%. Siete (41,2%) de estos pacientes tuvieron una tasa de desaparición de menos de 25%. Cuando una lesión es muy grande (40 cm^2 o más), la disminución media en el tamaño fue inicialmente pobre, pero la respuesta a los tratamientos posteriores fue constante.

En nuestro estudio se ha examinado si la edad de los pacientes tratados podría estar relacionada con la respuesta a los procedimientos de IPL. Se demostró que existía una asociación estadísticamente significativa entre la edad de los pacientes y la tasa de desaparición después del tratamiento con IPL.

Analizando los resultados obtenidos, se observó que en el grupo de menores de 18 años la tasa de desaparición de las lesiones en comparación con los adultos es mayor.

Una tasa de desaparición de más del 75% en el grupo de los más pequeños (menores de 1 año) fue observada en el 58,3% de los casos tratados (7/12), mientras que en el grupo de los adultos (mayores de 18 años) fue tan sólo del 8,7% (6/69). La tasa de desaparición del 50% al 75% es la más alta en el grupo de los niños de 1 a 6 años: 43,9% (18/41). La mitad de los pacientes (11/22) de edades entre los 6 y los 18 años tuvieron una tasa de desaparición de más de los 50%. En el grupo de los adultos (mayores de 18 años) el 63,8% (44/69) tuvo una tasa de desaparición del 25%-50%.

En el presente estudio se ha evaluado también la relación entre el número de tratamientos necesarios para lograr una tasa de desaparición máxima y la edad de los pacientes. Los pacientes fueron divididos en tres grupos por este motivo: (i) menos de 5 tratamientos, (ii) de 5 a 10 tratamientos y (iii) más de 10 tratamientos. El análisis estadístico fue llevado a cabo mediante la prueba exacta de Fisher y se encontró una relación estadísticamente significativa ($p < 0{,}001$) en el número de tratamientos efectuados en el grupo de los niños menores de 1 año y el grupo de los adultos.

El 75% (9/12) de los niños menores de 1 año necesitaron 5 o menos tratamientos para lograr los mejores resultados (más del 75% de desaparición) y ninguno de ellos necesitó más de 10 tratamientos. Por el contrario, en el grupo de los adultos sólo uno (1,4% (1/69) necesitó 5 o menos procedimientos y 72,5% (50/69) necesitaron más de 10 procedimientos.

Ciento cuarenta y cuatro pacientes en nuestro estudio fueron divididos en tres grupos según la manifestación clínica: (i) lesiones de color rosa, 57 casos (39.58%); (ii) lesiones de color rojo, 69 casos (47,92%); y (iii) lesiones con engrosamiento cutáneo, 18 casos (12,50%). En el grupo de las lesiones de color rosa el 89% (51/57) de los pacientes fueron menores de 18 años y el 11% (6/57) fueron mayores de 18 años. El sesenta y cinco por ciento (45/69) de los pacientes con lesiones rojas fueron adultos y el 35% (24/69) niños. No hubo niños en el grupo con lesiones con engrosamiento cutáneo.

En este trabajo se ha estudiado la posibilidad de encontrar una asociación entre el color de las lesiones y la tasa de desaparición de las mismas una vez realizado el tratamiento con IPL. El análisis estadístico (prueba exacta de Fisher, $p < 0{,}001$) mostró una relación estadísticamente significativa entre estos grupos.

Una tasa de desaparición de más de 75% fue más alta en el grupo de pacientes con lesiones de color rosa: 22,8% (13/57), seguido por los pacientes con lesiones de color rojo:14,5%. No hubo pacientes con resultado óptimo en el último grupo de lesiones con engrosamiento cutáneo. Se logró más de un 50% de desaparición de las lesiones en el grupo de pacientes con lesiones de color rosa: 40,4% (23/57), y 21,7% (15/69) en el grupo de los pacientes con lesiones rojas. Estos pacientes fueron denominados como como buenos respondedores a los tratamientos de IPL. En el grupo de las lesiones con engrosamiento cutáneo no hubo PWS que respondieran a los tratamientos con más de 50% de desaparición. En este grupo el 44,4% (8/18) de las lesiones mostraron un resultado subóptimo con una tasa de desaparición menos de 25%.

Se evaluó también la relación entre la localización de las PWS (cabeza, cuello y tronco o extremidades) y la eficacia del tratamiento. La prueba exacta de Fisher fue el método estadístico elegido para realizar este análisis. Se demostró una asociación estadísticamente significativa ($p < 0{,}001$) entre las dos variables. El 24,2% (23/95)

de las lesiones de la cabeza tuvieron la mayor mejoría media (tasa de aclaramiento de más del 75%) a diferencia de las lesiones del cuello y de las extremidades y el tronco donde no hubo ningún paciente dentro de ese porcentaje de mejoría. En el grupo de las PWS con localización del cuello el 46,4% (13/28) tuvieron una tasa de desaparición entre 50% a 75% y el 53,6% (15/28) tuvieron una tasa de desaparición de 25% a 50%. No hubo lesiones del cuello con desaparición de más del 75% y no hubo lesiones con una tasa de desaparición de menos de 25%. Aproximadamente el 57,1% (12/21) de las lesiones en las extremidades y tronco tuvieron alrededor de 25% a 50% desaparición y el 38,1% (8/21) tuvieron menos de 25% desaparición. En este grupo hubo tan solo un caso (4,8% (1/21) de PWS con tasa de desaparición entre 50% y 75% siendo el mejor resultado para dicho grupo.

Después de haber observado que las lesiones localizadas en la cabeza tuvieron mejor respuesta a los tratamientos de IPL, procedimos a evaluar si las diferentes unidades estéticas de la cabeza presentaban diferentes tipos de respuesta. Por ello la cabeza fue dividida en cuatro zonas: (i) la frente, (ii) la cara periférica, (iii) la cara central y (iiii) resto.

Los resultados obtenidos mostraron que las lesiones de la frente tuvieron la mejor respuesta a con los tratamientos con IPL. En este grupo el 92,9% (13/14) de las PWS tuvieron una tasa de desaparición más alta (más de 75%). Las lesiones faciales periféricas tuvieron muy buena respuesta: el 56,1% (23/41) tuvieron tasa de desaparición entre 50%-75% y ninguna de las lesiones presentó un porcentaje de desaparición de menos del 25%. En el grupo de lesiones centrales de la cara la tasa de desaparición fue inferior que en los dos grupos anteriores: el 67,9% (19/28) de las lesiones presentaron una tasa de desaparición de 25%-50% y el 25% (7/28) de ellos tuvieron una tasa inferior a 25%.

A lo largo del estudio pudimos observar que la ubicación de las PWS parecía tener alguna relación con la potencia que utilizábamos y el número de tratamientos. Se utilizó nuevamente la prueba de chi-cuadrado para determinar diferencias en estos supuestos

y encontramos una asociación estadísticamente significativa entre la localización de la lesión y la configuración energética empleada y el número de tratamientos.

Es decir, las lesiones localizadas en las extremidades necesitaron una energía más alta (más de 50J) y un mayor número de tratamientos (más de 10). En el grupo de lesiones de cuello en el 64,3% (18/28) de los casos, necesitaron una energía más baja (entre 30J a 40J) para obtener una respuesta efectiva. Las PWS con localización en la cabeza necesitaron menos procedimientos: el 40% (38/95) de ellos necesitaron 5 o menos sesiones.

Teniendo en cuenta que algunas de las PWS pueden reaparecer años después del tratamiento a pesar de obtener inicialmente una respuesta prometedora, pedimos a cada uno de los pacientes que habían terminado sus procedimientos que se presentaran en la consulta para seguimiento anual. Durante las visitas de seguimiento de nuestros pacientes pudimos observar que algunas de las PWS se habían tornado más oscuras en comparación con los resultados obtenidos al final del ciclo de tratamiento.

Habíamos observado que el 28,47% (41/144) de los pacientes presentaron una recurrencia entre una año y tres años después del tratamiento final. Las lesiones de 7 de los pacientes (17,1%) habían mostrado un tono más rojizo de uno a dos años después del tratamiento. Trece pacientes (31,7%) tuvieron recurrencia entre dos y tres años después del tratamiento y 21 pacientes (51,2%) después de más de tres años. Este hecho fue considerado como una recurrencia focal y pudimos constatar que con un tratamiento nuevo mejoraba significativamente el aspecto de la lesión.

En nuestro estudio habíamos encontrado que sólo 1 de los 12 pacientes (8,33%) menores de un año tuvieron recurrencia después del final de su tratamiento. En el grupo de niños de entre 1 a 6 años, sólo 5 de 41 (12,20%) tuvieron lesiones más oscuras posteriormente. Seis de 22 (27,27%) niños de 6 a 18 años tuvieron una recidiva. Al contrario que en los grupos de niños, la tasa de recurrencia en el grupo de adultos (mayores de 18 años) fue mucho más alta: 29(42,03%) de 69 pacientes.

Se utilizó la prueba de chi-cuadrado para analizar si hubo asociación estadísticamente significativa ($p < 0{,}001$) entre el color de las PWS y su recurrencia. Se pudo observar que sólo un 7% (4/57) de las lesiones de color rosa presentaba recurrencias, en comparación con un 30,4% (21/69) en las de color rojo y un 88,9% (16/18) en las lesiones con engrosamiento cutáneo.

5. Conclusiones

1. La luz intensa pulsada es un método eficaz para el tratamiento de las manchas rojo-vinosas con diferentes localizaciones anatómicas en pacientes de diferentes edades y tipos de piel.

2. Las manchas rojo-vinosas con un tamaño menor (menos de 20 cm^2) presentan una mejor respuesta al tratamiento con luz intensa pulsada que las lesiones grandes, con independencia de la edad del paciente.

3. La tasa de desaparición de las manchas rojo-vinosas después del tratamiento con luz intensa pulsada disminuye conforme mayor es la edad del paciente.

4. El número de las sesiones necesarias de tratamiento con luz intensa pulsada aumenta cuanto mayor edad presenta el paciente.

5. La tasa de desaparición de las manchas rojo-vinosas tratadas con luz intensa pulsada varía según su localización anatómica: las lesiones en la cabeza parecen mostrar una mejor respuesta al tratamiento en comparación con las de localizaciones no faciales, siendo la frente la zona donde las lesiones tienen la mejor respuesta en comparación con las lesiones del resto de la cara.

6. La tasa de recurrencia de las manchas rojo-vinosas tratadas con luz intensa pulsada se ve incrementada cuando el color de las lesiones se vuelve más oscuro y la edad del paciente aumenta. En pacientes con lesiones más claras y de menor edad, la tasa de recurrencia tras el tratamiento con luz intensa pulsada es menor.

INTRODUCTION

1. INTRODUCTION

Vascular lesions are a heterogeneous group of anomalies which differ in both their clinical presentation and histopathological features. The adequate diagnosis is of paramount importance because of their distinct differences in morbidity, prognosis, and treatment.

Cutaneous vascular malformations, comprising a significant part of the vascular lesions, are rare disorders representing errors in vascular development that occur in approximately 0.3% to 0.5% of the population (1,2). These lesions are often confused with the common vascular birthmark-infantile hemangioma although they are much less frequently seen.

1.1. Vascular Malformations- Concepts and Classifications

By the use of confusing terminology and classifications, the identification of vascular anomalies was historically hampered. For a long period of time, the use of an inaccurate nomenclature has led to confusion. For example, capillary hemangioma, nevus flameus, and port-wine stain (PWS) have all been used in the literature to describe a capillary malformation of the skin (1,3). Since management of this heterogeneous group of lesions depends on the specific vascular malformation, a proper classification and identification is critical. Thus, a brief review of the changing concepts and classifications is of practical and scientific importance for any further study and commentaries (4).

In 1863 Virchow and Wagner in their early published classifications characterized vascular lesions according to the vessel's pathologic appearance (5). Vascular growths were divided into angiomas (simplex, cavernosum, and racemosum) and lymphangiomas (simplex, cavernosum, and cystoides).The natural history and the biologic behavior of the vascular lesions were not considered and there was a tendency to identify any vascular anomaly as a hemangioma.

A main step along the difficult path to clarity was the publication of Mulliken and Glowaschky in 1982, which divided vascular birthmarks into two major categories: hemangiomas and malformations. This classification was groundbreaking and has served as a cornerstone for the proper identification, investigation, and management of vascular birthmarks (6). Hemangiomas were differentiated from vascular malformations by their clinical appearance, histopatologic features and biologic behavior. Vascular malformations had an equal sex distribution, whereas hemangiomas were found to be more common in girls. The natural history of hemangiomas involved rapid proliferation for the first several months of life with subsequent spontaneous regression, often leaving fibrous fatty deposition, overlying anetoderma, and telangiectases. Vascular malformations are often recognized at birth and grow proportionately with the child, with many becoming more prominent at puberty. One of the most commonly seen in the daily practice type of vascular malformations are the Port Wine Stains (PWSs) which have all typical features of the group of vascular malformations (Table 1) (1,15).

Mulliken's biologic classification has been widely adopted by clinicians to differentiate vascular birthmarks and is the accepted classification of the International Society for the Study of Vascular Anomalies (ISSVA). In 1996, the classification was modified slightly to reflect the importance of other types of vascular tumors that exhibit different clinical and histologic characteristics than the common infantile hemangioma, including kaposiform hemangioendotheliomas, tufted angiomas, and others. Consequently, the updated ISSVA/biologic classification divides vascular birthmarks into vascular tumors and vascular malformations. This classification is useful for managing patients and provides a framework for study of these lesions (Table 2) (11).

Pediatric vascular lesions	Hemangiomas	Port-wine stains
Origin	Absent or small at birth. Grow rapidly in early infancy. Unclear origin: possibly a first-trimester developmental error regarding vasculogenesis and/or angiogenesis or a result of embolized placental cells. Possible autosomal dominant inheritance (7).	Present at birth. Grow in proportion to child's growth. Unclear origin: possibly a result of vascular channel developmental defects or segmental deficiency of autonomic innervation of postcapillary venules.
Prevalence	Affect 1.1%-2.6% of newborns. Usually develop after birth. Affect 10% of Caucasian children within first year (8,9). Three times more common in female than male patients (8). More common in premature infants. Higher prevalence in infants of mothers postchorionic villus sampling.	Affect 0.3%-0.5% of newborns (10). Equal prevalence in male and female patients. No significance between premature and full-term infants (8). Associated with Sturge-Weber and Klippel-Tre´naunay syndromes. Very rare late onset in adolescents and adults, usually caused by trauma (11).
Diagnosis	Superficial, deep, or mixed vascular tumors. Histology shows plump endothelial cells (7). Specific growth and involution phases. Many hemangiomas spontaneously disappear, others grow to disfiguring sizes. Ulceration is possible.GLUT1 positive.	Vascular malformation. Usually well defined (12) red macular stains. Histology shows flattened endothelium (13). Slow growth throughout lifetime. No regression or ulceration. GLUT1 negative.
Who requires treatment	Treatment is controversial because of unpredictable growth of hemangiomas. Life- or function-threatening lesions, lesions in locations that will permanently scar and ulcerated lesions are high priorities for treatment.	All patients require treatment, because of the expansive nature of PWSs, and their tendency to cause psychologic problems (14).
Treatment types	Systemic and direct corticosteroids, vincristine, recombinant interferon alfa-2a and -2b, imiquimod, surgery, laser treatment, cryotherapy, active non-intervention	Laser treatment, plus surgery for individual nodules and soft-tissue hypertrophy, and orthodontic management for complications (11).

Table 1. Comparison between hemangiomas and port wine stains.

Vascular tumors	Vascular malformations	
	Simple	Combined
Infantile hemangioma	Capillary	AVF, AVM
Congenital hemangioma	Lymphatic	CVM, CLVM
Tufted angioma	Venous	LVM, CAVM
Kaposiform hemangioendothelioma	Arterial	CLAVM
Hemangiopericytoma		
Pyogenic granuloma		
Spindle-cell hemangioendothelioma		
Spindle-cell hemangioendothelioma		

Table 2. Vascular anomalies: ISSVA/Mulliken classification 1996. *Used abbreviations: AVF,*

Arteriovenous fistula; AVM, arteriovenous malformation; CAVM, capillary AVM; CLAVM, capillary-lymphatic AVM; CLVM, capillary-lymphatic venous malformation; CVM, capillary venous malformation; LVM, lymphatic venous malformation.

Beginning in 2013, a group of ISSVA leaders from both the scientific committee and board, with mindful consideration given to the various existing classifications, sought to update and improve the classification of vascular anomalies, both to make it more clinically relevant and flexible and to knowledge new genetic and histologic information available since its 1996 classification was approved. This updated consensus classification is intended to be applicable and functional for all medical and surgical specialties and for every organ or tissue. Because the updated classification lists a large number of different diseases, it is presented as a general table containing the main classes of vascular anomalies (Table 3) (15).

Vascular malformations can be further subdivided into groups on the basis of their vascular components and flow characteristics. They may be composed of slow-flow capillary, venous, or lymphatic channels, fast-flow arterial channels, or a combination of each (Table 4) (1).

Vascular tumors	Vascular malformations			
	Simple	Combined	of Major Named Vessels	Associated anomalies
Benign Locally aggressive or border-line Malignant	Capillary syndrome	AVF, AVM		Klippel-Trenaunay
	Lymphatic syndrome	CVM, CLVM		Parkes-Weber
	Venous syndrome	LVM, CAVM		Sturge-Weber
	Arterial	CLAVM		

Table 3. 2014 ISSVA Classification of Vascular Anomalies. *Used abbreviations: AVF, Arteriovenous fistula; AVM, arteriovenous malformation; CAVM, capillary AVM; CLAVM, capillary-lymphatic AVM; CLVM, capillary-lymphatic venous malformation; CVM, capillary venous malformation; LVM, lymphatic venous malformation.*

Slow flow	Fast flow
Capillary malformations - Port-wine stains - Telangiectases Venous malformations Glomuvenous malformations Lymphatic malformations - Macrocystics - Microcystics Combined - CLM (angiokeratoma) - CLVM - CMTC (CVM)	AVMs Combined CAVM

Table 4. Vascular malformations by flow characteristics and vascular components.

Used abbreviations: AVM, Arteriovenous malformation; CAVM, capillary AVM; CLM, capillary-lymphatic malformation; CLVM, capillary-lymphatic venous malformation; CMTC, cutis marmorata telangiectatica congenital; CVM, capillary venous malformation.

1.2. Pathogenesis of Vascular Malformations.

The pathogenesis of vascular malformations is not yet well understood. It is speculated that they arise as a result of abnormalities in the process of normal vascular development. The normal vascular system arises during embryogenesis via two processes: vasculogenesis and angiogenesis. Vasculogenesis refers to the process by which vascular channels are formed "de novo" from endothelial cell precursors (angioblast). Angiogenesis refers to the development of new vessels from preexisting vasculature (16-20). Recent studies have provided some insight into the complex processes of normal vasculogenesis and angiogenesis, suggesting that errors result in abnormal vascular channels and vascular malformations (17). Moreover, the investigation of rare inherited forms of familial vascular malformations has enabled investigators to study how specific disruptions in the normal process of vascular development, caused by genetic abnormalities, may result in these skin lesions.

1.3. Capillary Malformations of the Skin. Port Wine Stains

Capillary malformations (CMs) include port wine stains (PWS) and telangiectasias. They are among the most common vascular malformations affecting the skin (18). These slow-flow vascular anomalies occur in approximately 3 of 1000 infants and have an equal sex distribution. However, familial cases have been described, they usually arise sporadically (3, 22-23). Port wine stains are usually noted at birth, but may initially be misdiagnosed as erythema or a bruise from birth trauma. They may be single or multiple lesions and present as small patches or involve an entire limb or portion of the face. These capillary malformations may arise on any surface of the skin, but are frequently presented on the head and neck area (Figure 1).

Figure 1. Infant with facial CM: "Port-wine stain".

They may extend to the lips, gingiva, or oral mucosa when they are located on the head. CMs are usually pale pink macules and patches in young infants (1).

The clinical behavior of port wine stains varies according to their anatomic location. The terms "salmon patch", "angel's kiss", "stork bite", "nevus simplex", and "vascular stain" are used to describe a subset of CMs that are very common and located on the central area of the face (glabella, eyelids, nose, and upper lip) and the nape of the neck. Vascular stain in glabella region- Angel's kiss type (Figure 2), typically fades with maturity. Sometimes they are termed "fading macular stains" rather than true CMs because these lesions typically lighten significantly or disappear within the first few years of life (2). Some, particularly those on the nape of the neck, persist into adulthood without significant darkening.

Figure 2. Vascular stain in glabella region: "Angel's kiss type".

Salmon patches may also be located in the midline sacral region and have been called

butterfly-shaped marks and sacral telangiectatic nevus. In contrast, as the patient matures, true facial CMs may become darker, more violaceous, thicker, develop blebs, and in some cases, become hyperkeratotic. Limb and trunk port wine stains may appear to be very red at birth and sometimes fade to a lighter pink over time.

PWS are usually isolated lesions, but some of them could be associated with serious syndromes that must be recognized in a timely fashion. These include Sturge-Weber syndrome (19), Klippel- Trenaunay syndrome (20), and other less common constellations of findings.

- Sturge-Weber syndrome comprises of a large facial PWS (Figure 3) with ipsilateral leptomeninigal vascular malformation, ipsilateral choroidal vascular malformations, and glaucoma.

Figure 3. Infant with facial PWS and Sturge-Weber syndrome.

The distribution of facial PWS along the ophthalmic (V1) distribution of the trigeminal nerve is determinant of central nervous system or ocular anomalies (19). Patient with V1 distribution PWS are further divided into “high risk” and “low risk” group. Patients at high risk for Sturge-Weber show involvement of the entire V1 area with or without V2

and V3. Low risk patients have incomplete involvement of V1 with or without V2 and V3 involvement. There is no risk of neuro-ocular anomalies in patients with V2 and V3 distributed PWS in the absence of V1 involvement, and these individuals require no further medical workup. There is a significantly higher incidence of glaucoma and / or central nervous system abnormalities associated with eyelid PWS, bilateral trigeminal branches (24,26). Children with PWS in these distributions should undergo appropriate testing for central nervous system and ocular abnormalities. Ophthalmic examination is recommended twice annually until the age of two and yearly thereafter, as glaucoma may have a later onset (25,27).

- Klippel-Trenaunay syndrome constitutes a capillary-venous vascular malformation accompanied by hypertrophy of the affected limb of body part. Clinically, the findings may range from barely noticeable limb discrepancy to debilitating limb asymmetry requiring wheel chair confinement. The cutaneous capillary malformations may be patchy on the involved leg, and can be associated with hemolymphatic vesicles. There may be associated anomalous superficial veins, deep vein hypoplasia, and lymphatic malformations (20). Leg involvement is the most common presentation of the syndrome (Figure 4).

Figure 4. Klippel–Trénaunay syndrome.

One study showed greater predominance of right sided lesions (21). Complications of

Klippel-Trenaunay syndrome include thrombosis, coagulopathy, pulmonary embolism, heart failure, or bleeding from abnormal vessels in the genitalia, gut, or kidney. Patients generally undergo annual noninvasive vascular imaging adding limb girth measurements if there is clinical evidence of asymmetry. Lesions that extend to the pelvis or trunk can cause hematuria or hematochezia and warrant evaluation with noninvasive imaging and endoscopy. Shoe lifts are commonly used for leg discrepancies greater than 1.5 cm, and compression garments are useful for limbs with venous insufficiency or bleeding from superficial vesicles. Severely hypertrophic limbs may require surgical debulking or limb length adjustment (25, 28).

PWS may also be present in a number of other rare syndromes. PWS in the sacral area may indicate occult spinal dysraphism, lipomeningocele, or a tethered cord (22). These lesions require further workup. Other associated syndromes include Parked-Weber syndrome (25, 30), Cobb syndrome (30-32), Proteus syndrome (33-35), and phakomatosis pigmentovascularis (36-37).

1.3.1. Pathogenesis of Port Wine Stains

Port wine stains are believed to represent an error in vascular development occurring during embryogenesis. Histopathology reveals an increased number and ectasia of blood vessels in the dermis (Figure 5).

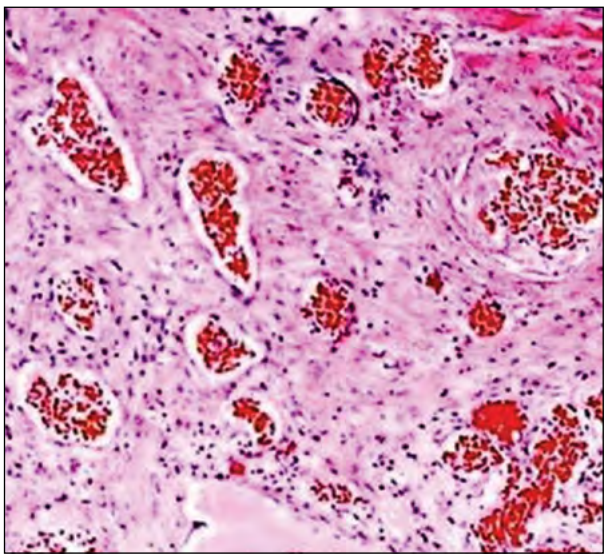


Figure 5. In port wine stain the dilated vessels extend intodeeper dermis and may involve the subcutaneous tissue.

The majority of the vessels of a CM are located in the papillary and reticular dermis

with number of anomalous vessels decreasing with increasing depth. Although early studies estimated a mean depth of 0.46 mm, subsequent studies have demonstrated variability in vessel depth that is dependent on location of the lesion. Some studies have suggested that lesions in the V3 dermatome neck and trunk region tend to be more superficial, whereas lesions in the V2 dermatomal area and distal extremities have more deeply placed vessels (1,38). Vessel number and depth correlate poorly with age; however, the mean vessel are and percentage of fullness increase with age. This accounts for change in color of the lesion from pink to violet with maturity. It is noticed that this correlation is not complete, and younger patients may show features that are more characteristic of "mature" port wine stains (26). The variability accounts for the differences in response to pulsed-dye laser (PDL) treatment. Immunohistochemical analysis has demonstrated number of neurons associated with the ectatic vasculature in port-wine stain (27). There is a hypothesis that an alteration in the neural modulation of vascular flow may be involved in the pathogenesis of these lesions. Alternatively, the reduced density of neuronal cells may be secondary to abnormal vasculature and relative ischemia (40-42).

Several proteins and receptors integral to vasculogenesis and angiogenesis have been proposed to cause vascular malformations but only a few of them have been linked to CMs specifically. There are several reports of autosomal dominant familial cases of CMs associated with arteriovenous malformations (AVMs), identifying locus CMC1on chromosome 5q as the genetic region involved (29). Further genetic mapping has identified RASA1, encoding p120-rasGTPase-activating protein (p120-rasGAP), as the causative defect. p120-rasGAP appears to be integral to signaling for various growth factor receptors that control proliferation, migration, and survival of several cell types, including vascular endothelial cells (30). Another protein knows as developmental endothelial locus-1 (Del-1) may also play a role in some cases of CM. Del-1 is an extracellular matrix protein adhered to by human umbilical vein endothelial cells that has been shown to induce formation of a vascular plexus with a high number of small capillaries (31). For the majority of patients

with CMs, however, the molecular pathogenesis has yet to be elucidated.

1.3.2. Diagnosis of Port Wine Stains

Port wine stains are diagnosed on the basis of their clinical appearance (32). It is important to note that cutaneous erythema overlying a deeper arteriovenous malformation (AVM) may mimic a CM. Doppler ultrasound evaluation is useful but not always diagnostic in suspected cases to detect an arteriovenous fistula or shunt (33). Once the diagnosis of port wine stain is established, the patient should be carefully examined for the presence of underlying vascular malformations and associated congenital anomalies. Studies such as magnetic resonance imaging (MRI) , Duplex Doppler Scan, lymphoscintigraphy, bone x-rays, and even arteriography may be necessary in a minority of case to evaluate for an underlying or associated anomaly (1).

MRI is the most informative investigation which can determine the extent of a vascular lesion with a high degree of accuracy as well as distinguish between the different types of malformation, but it is usually not necessary in the investigation of port wine stains. It is indicated only if you suspect e.g. meningeal involvement (34).

1.3.3. Treatment Options of Port Wine Stains

Port wine stain was considered to be essentially untreatable until the advent of argon laser. From the beginning a frequent therapy was vaccination in and around the PWS or injection of the “hospital pus” (47,48). Treatment techniques have included the most inappropriate applications of radiation, either by external radiotherapy or the application of thorium X (35) or radioactive phosphorus (36). At best this appeared to have had no particular benefits, and at worst these applications may have been responsible for malignant changes, radiodermatitis and bony hypoplasia which authors have been seen in previously radiated PWS (37). Other treatments have included Bucky (=Grentz) ray, sclerosing agents, cauterization, cryo therapy, carbon dioxide snow, liquid nitrogen, cortisone, protamine, heparin locally and systemically,

obliteration by ligature of vessels, ultraviolet and infrared radiation and dermabrasion (38). All these techniques usually have replaced the PWS with scarring and pigment changes. In many cases some of the red color was only replaced by disfiguring scars.

Tattooing the port wine stains with masking pigment has been tried , but does not seem to have been widely practiced or with much success (39) and it is not recommended today, when we have the expanding development of vascular lasers.

Another attempts to treat port wine stain is surgery by rotation of flaps, excision and skin grafting, but it has been difficult to achieve a natural texture and color of the skin (40). Post-surgery scarring is not well acceptable especially regarding lesions located in the face.

Both men and women with port wine stains very often have a need to conceal their lesions and they use cosmetic camouflage. Its application is time consuming and not always successful or appropriate.

1.3.3.1. Treatment of Port Wine Stains with Light Devices

Nowadays the standard treatment for PWS is laser therapy (41). In the 1960s Leon Goldman and colleagues started the era of laser dermatology with preliminary studies of the skin with the help of a CO_2 laser. He was later called "the father of laser medicine in the United States" and in 1979 he became one of the founders of the American Society of Laser in Medicine and Surgery (34).

In the early 1980s Noe et al performed controlled studies on the use of argon laser to treat PWS. Many therapeutic methods have been used to treat PWS and most of these methods, including older lasers, have been abandoned due to ineffectiveness or adverse effects such as scarring. In 1983 the important work on selective photothermolysis by Anderson and Parrish was published (42). Since then, rapid development have provided lasers that could be coupled to an optical fiber, efficient detector arrays and advanced computers for control of medical instrumentation. The medical and surgical applications of lasers and intense pulsed light sources have continued to progress along several lines including research, diagnostics and therapeutics (34).

Among the various lasers used for treating port wine stains, pulsed dye laser (PDL) has the best efficacy and safety data (43). The other machines that are widely available are Nd:YAG laser, KTP laser and intense pulse light (IPL) (44).

1.3.3.1.1. Principles of Laser Tissue Interaction

It is very important to have a practical understanding of laser-tissue interaction because laser technology now has reached a point where we can routinely use high energy devices to perform treatments that were impossible some years ago. All effects of light begin with the absorption of electromagnetic radiation (EMR), which is fundamental form of energy that exhibits wave properties. This wave is caused by alternating electric and magnetic field. The energy is carried in quanta known as photons. Electromagnetic radiation is absorbed by matter through interactions with charged particles such as electrons or the partial separation of charges in molecules called dipoles (45).

LASER= **L**ight **A**mplification by **S**timulated **E**mission of **R**adiation

Atoms and electrons are normally in a "resting state". If an electron absorbs energy of a photon of light, the electron is raised to an "excited" state. This "excited" electron can give up its energy by emitting a photon of light energy identical to the photon that was initially absorbed. If an "excited" electron absorbs a photon of light energy, this electron may emit two photons of light energy while the electron returns to the resting state (=stimulated emission of radiation). Repeating this innumerable times generates a powerful laser beam (46). Absorption and excitation are necessary for all photobiological effects and laser tissue interactions. A lasing medium can be either gaseous, liquid, solid crystal or semiconductor. The external energy source can be electrical, chemical, flashlamp or light from another laser.

Laser light has 4 main properties (47):

- Monochromaticity – a single wavelength of all of the lights due to the determination of the laser medium present in the optical cavity. All of the chromophores in the skin such as melanin, hemoglobin or tattoo ink selectively absorb laser light with a specific wavelength.

- Brightness (intensity) – due to the tremendous amplification process available in the laser cavity extremely high power can be generated with lasers
- Coherence - this is the synchronicity in time and space of the photons emitted from lasers. It implies that the passing waves have nearly identical and parallel wavelengths with low degree of divergence. Therefore, there is no significant loss of intensity (48).
- Collimation - this is the same as parallelism of light as a direct result of coherence. It allows the beam to propagate across long distances along optical fibers without beam spreading.

There are several interactions of light according to Rox Anderson (45). Absorption and scattering are the two most fundamental interactions.

- Absorption – occurs when the photon surrenders its energy to an atom or molecule, known as a chromophore. The absorption spectra of major skin chromophores dominate most laser-tissue interactions in dermatology. The photon cease to exit and the chromophore becomes excited and may undergo photochemistry or may dissipate the energy as heat or reemission of light. Blood absorption is dominated by absorption of oxyhemoglobin and reduced hemoglobin, which inhibits strong band in the UV, blue and green and yellow bands, with absorption peaks at 418, 542 and 577 nm (Figure 6).

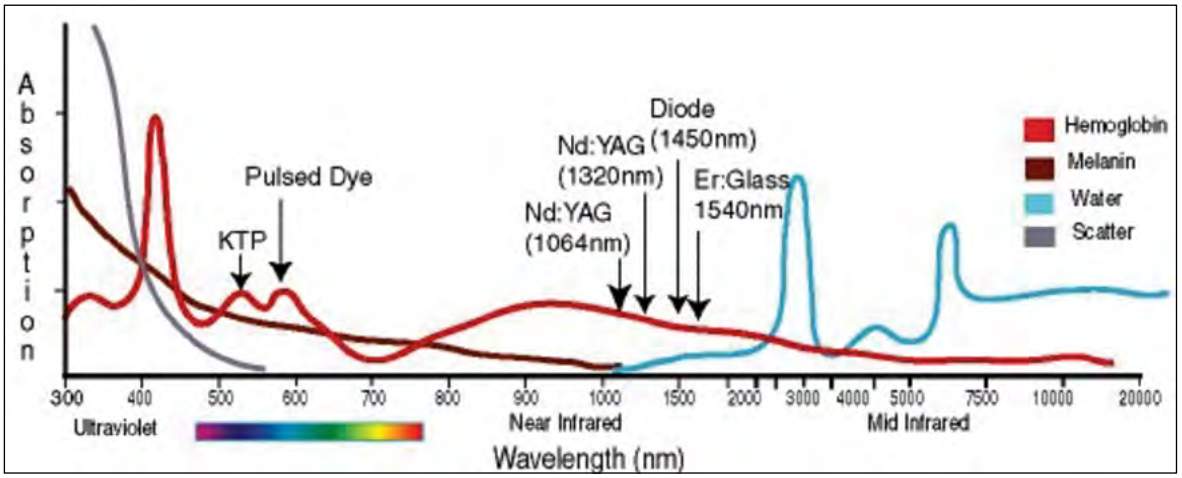


Figure 6. Absorption spectra of the main chromophores in the skin.

- Melanin, in epidermis and in the hair follicles, is the major chromophore and it absorbs broadly across the optical spectrum (320-1200 nm) Therefore the pigmented epidermis could be a barrier to the photons and cause significant epidermal damage leading to non-specific thermal injury (62).

- Scattering - is when the photons change direction. The light that is returning from the skin is scattered light and a strong scattering contributes towards reducing the optical penetration depth (49). Optical penetration into dermis is largely dominated by the scattering caused by collagen fibers. Because light scattering in the dermis decreases with increasing wavelength, greater light penetration is achieved at longer wavelengths. Back scattering may actually increase the power density of the laser beam. Forward and sideways scattering will attenuate the power density of the incident beam with depth.

- Reflection - a reflection of 4% of the incident irradiation can be caused by the different refractive indices of stratum corneum and air and will give no clinical effect (49).

- Transmission - light can be transmitted through the target tissue such as the dermis without any clinical effect. In white epidermis the transmission of light increases from about 50% at 400 nm to 90% at 1200nm (45). Less than 20% throughout the visible spectrum will be transmitted in black epidermis. For wavelengths shorter than 600 nm (with the high absorption of hemoglobin and melanin) there will be hardly any transmission of visible light in dermis.

1.3.3.1.2. Laser Therapy of Port Wine Stains

Laser therapy is the standard treatment for PWS (60). As it has been stated before, the basic principle of the laser therapy is the preferential absorption of laser light by hemoglobin and the subsequent conversion of the absorbed light into thermal energy

that leads to the coagulation of blood vessels (50). Selectivity and spatial confinement to spare the tissue surrounding blood vessels is achieved by selecting an appropriate wavelength, pulse duration, spot size, and fluence (47-51,55,62)- a process called selective photothermolysis (SP) (42). Because of its proven efficacy and low incidence of side-effects, the pulsed dye laser (PDL) with a wavelength of 585 nm and a pulse duration of 0.45 ms was initially the method of choice for the treatment of PWS (49-53,63,64). Over the past two decades, important advances include the use of longer wavelengths of 585-600 nm and longer exposure times (54). The addition of surface cooling enables the delivery of higher fluences without epidermal damage (55). Although clinical results are excellent for many patients, multiple treatments are necessary to achieve maximal lightening; furthermore, complete clearing of PWS is rare (62, 66). Moreover, about 20-30% of PWS are resistant to PDL treatment (56). Thus, various other laser devices have been introduced for the treatment of PWS (57). In Table 5 are shown different types of lasers and intense pulsed light sources which can be used in the treatment of PWS according to the type of the lesion and the size of the vessels which they are consisted of (58).

Type of PWS	Laser of choice
Earliest, smallest vessels, 50-80 μm. Light and dark pink macules	PDL, KTP, IPL
Clearly indistinguishable, more advances, 80-120 μm with individual vessels clearly visible to the bare eye	PDL (long pulse), KTP, IPL
Reddish patches with vessels even more ectatic, 120-150 μm	PDL (long pulse), KTP, IPL
Thick, purple, palpable, possibly nodular advanced dilated vessels > 150 μm	IPL, Nd:YAG

Table 5. Choice of lasers in PWS. *Used abbreviations: PDL- pulsed dye laser, KTP-Potassium titanyl phosphate, IPL-Intense pulsed light; Nd:YAG- neodymium-doped yttrium aluminium garnet.*

- **Flashlamp-pumped Pulsed Dye Laser (PDL)**

Introduced in 1980s, the flashlamp-pumped dye laser (PDL) was the first instrument to implore the concepts of selective phototermolysis (Figure 7) (59).

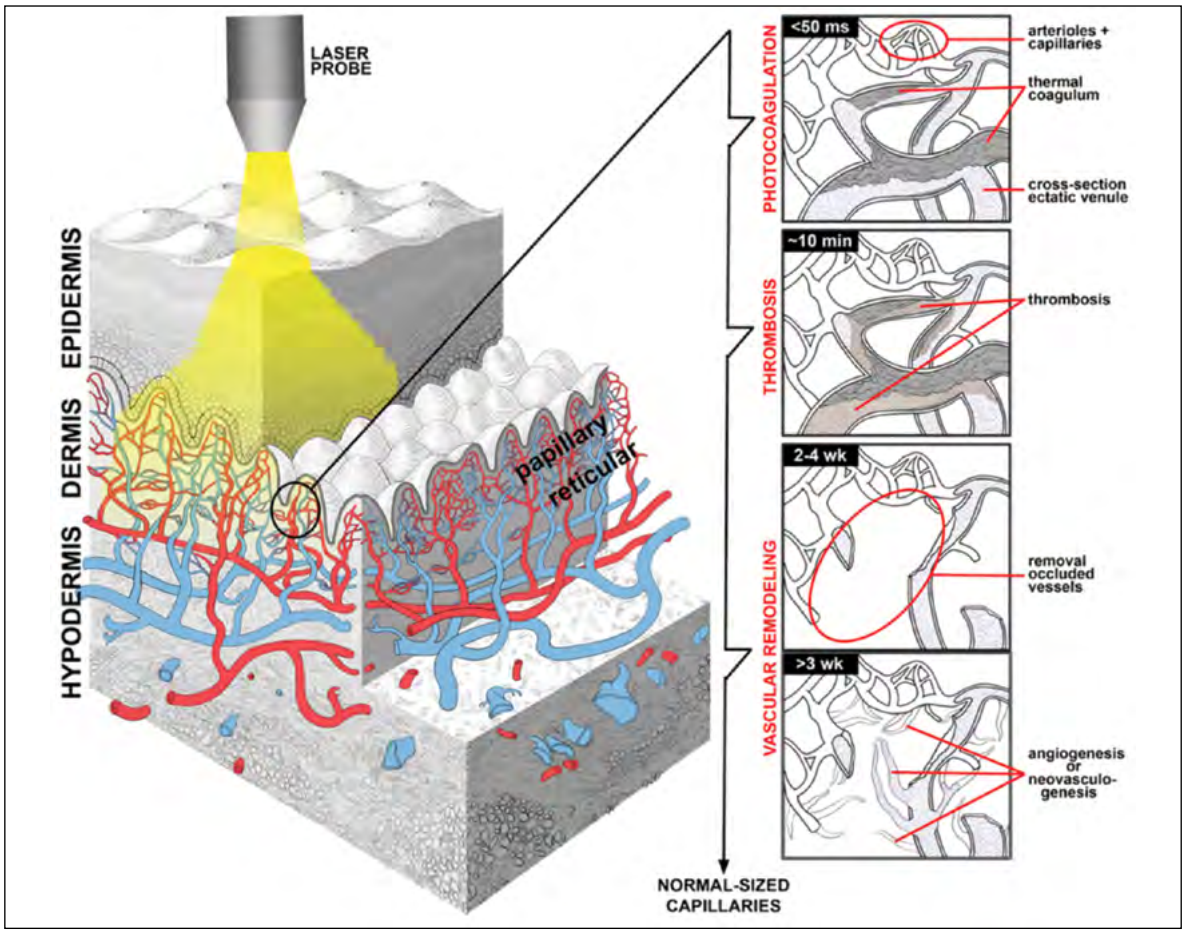


Figure 7. Overview of endovascular laser-tissue interactions in pulsed dye laser (PDL) treatment of refractory port wine stain (PWS) skin. *Yellow light-emitting PDL is used to selectively photothermolyze ectatic venules (blue structures) in predominantly papillary dermis* (66).

A wavelength of 577 nm was initially chosen to provide strong absorption by oxyhemoglobin present within the blood vessels and reduced absorption by melanin in the surrounding tissue (18). The laser wavelength was subsequently increased from 577 to 585 nm to provide increased depth of penetration in tissue and improve clearance of PWS (60). Early pulsed dye laser systems used for studying PWS treatment used pulse dura-

tions ranging from 300 to 500 µs. Since the late 1980s the commercially available pulsed dye lasers have been manufactured with a wavelength of 585 nm and a pulse duration of 450 µs. In histological studies, pulsed dye laser treatment produces intravascular thrombosis formation without epidermal or dermal damage (61). Approximately 1 month after treatment, normal appearing vessels replace the ectatic lesional vessels.

Damage to vascular tissue is so selective with pulse dye laser that there is inconsequential absorption by melanin in fair-skinned individuals (62). The laser can be safely used in skin types I-III and photo type IV when there is no suntan present (63). Pulsed dye laser cannot be used to treat skin types V and VI because the higher density of melanin results in decreased vascular absorption and the possibility for epidermal damage (64). Newer studies of cryogen-cooling techniques throughout the pulse sequence suggest that safe treatments of darker skin phototypes may be possible in the near future (65).

Even if approximately 30% of PWS seem to be resistant to PDL treatment, PDL are still the treatment of choice for macular PWS, and are considered the *"gold standard"* in the therapy of these lesions (62, 76- 79). In general, PDL parameters are as follows: 585–600 nm wavelength, 5–18 J/ cm^2 fluence, 0.45–10 ms pulse duration, and a spot size of 5–10 mm (83).

- **Potassium Titanyl Phosphate (KTP) Laser**

The KTP laser emits green light at a wavelength of 532 nm. The KTP laser may be used to further lighten PDL-resistant PWS. Chowdhury and colleagues (68) treated 30 patients who had previously experienced less than 50% lightening during at least five sessions of PDL therapy (mean: 15.5 sessions). Overall, 53% of patients showed more than 25% response and 17% showed more than 50% response to KTP laser treatment (532 nm,18–24 J/cm^2, 9–14 ms, spot size not noted). As adverse effects, transient hyperpigmentation, hypopigmentation, and hypotrophic scarring were noted in 1–2% of

patients. In conclusion, KTP lasers are safe and effective alternatives that may raise the success rates in PWS refractory to other laser therapies. However, the small spot size of KTP lasers limits its use in larger PWS.

- **Alexandrite Laser (755 nm)**

The 755-nm alexandrite laser has been shown to effectively treat hypertrophic or nodular lesions, which may be associated with deeper blood vessels (81 - 84). This laser system has proven particularly useful in the treatment of hypertrophic and PDL-resistant PWS (81, 85), especially when used in conjunction with the PDL. A study on the PDL/ alexandrite laser dual approach (λ = undisclosed wavelength/755 nm) demonstrated significant lightening in all of 3 patients with hypertrophic PWS and moderate lightening in 12 of 17 patients with PDL-resistant PWS (70).

The therapeutic efficacy of the alexandrite laser has been attributed to several factors. First, the 755-nm wavelength falls inside the therapeutic window: with less absorption by melanin as compared to yellow wavelengths, light is able to penetrate more deeply into tissue. Second, the 755-nm wavelength is more strongly absorbed by deoxyhemoglobin than by oxyhemoglobin, and in theory should preferentially damage venules (ie, PWS vasculature) over arterioles (66).

However, longer wave-length lasers are associated with elevated risk of adverse events such as pigmentary changes and scarring, owing to the deeper tissue penetration and decreased absorption by hemoglobin, which necessitates the use of higher fluences. In the case of the alexandrite laser, it has been recommended to treat only until achieving a subtle gray-blue darkening of the skin that, within several minutes, evolves into deeper purpura (71). The fluence threshold for such a response is best determined in the darkest PWS area, where this threshold is lowest.

- **Neodymium:Yttrium-Aluminum-Garnet Lasers (1064 nm)**

As with other longer wavelength lasers such as the alexandrite laser, the 1064-nm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser can further reduce optical scattering and melanin absorption. Promising results have been obtained especially in purple, hypertrophic, and nodular PWS lesions (72). Yang et al. (73) reported that this laser system was as effective as the PDL for treating PWS when used at the minimal purpura dose, and our group has achieved relatively high clearance rates in specific patient cohorts.

As with the alexandrite laser, because of the lower hemoglobin absorption and relatively high water absorption at 1064 nm, higher fluences are required for sufficient photocoagulation, concomitantly causing nonselective bulk heating (74). Thus, the 1064-nm Nd:YAG laser can result in significant scarring when using fluences greater than 1.2 times the minimal purpura dose (73). This makes safe treatment of anatomically heterogenous vascular lesions such as PWS difficult. Moreover, the therapeutic response and tolerance varies greatly among PWS lesions, which further limits the use of the 1064-nm laser in general practice. Such therapy is best performed by those with experience with these devices (75).

- **Intense Pulsed Light (IPL) in Therapy of Port Wine Stains**

These devices emit polychromatic incoherent high-intensity pulsed light with an emission spectrum ranging from 400 to 1400 nm and pulse durations in the millisecond range. Theoretically, IPL systems have a potential advantage over other laser systems because they incorporate the highly oxyhemoglobin selective wavelengths around 577 to 600 nm and also emit longer wavelengths allowing deeper penetration into the dermis and deeper capillary destruction (85, 87).

The greatest difference in comparison to lasers is that IPL simultaneously delivers multiple light wavelengths at a different intensity; for this reason, IPL has been considered a virtual application consisting of numerous lasers simultaneously emitting different

wavelengths and radiant light exposures (J/cm^2). By selecting a cut-off filter, the physician is able to choose the wavelengths that will be emitted above that point, to match and destroy a specific target structure.

The IPL device consists of a flash-lamp housed in an optical treatment head, in which reflecting mirrors are designed to deliver the light through an optical waveguide. The flash-lamps are normally water cooled in order to minimize the lifetime of the lamp and enable the system to deliver high output energy. Some technologies use interchangeable, "snap in" quartz waveguides to transmit the light to the skin. In most designs, these quartz waveguides are coated with a dielectric (multilayer, reflecting) coating. Although a dielectric coating is very efficient in reflecting of the output from the flash-lamp. Newer technologies now incorporate a dual filtration method (patient pending- Palomar Medical Technologies) which employs both a dielectric reflective coating and an absorption coating surrounding the lamp. With this innovation, IPL technology begins to mimic the selectivity of laser systems. Since the evolution of the IPL from 1995, the technology has developed from low energy, nonselective units, to high energy, very selective and clinically effective devices. There are approximately 20 types of competitive units in this market place, however, most are low energy units (56,66-77,88).

- **Wavelength**

When unfiltered, the IPL device is capable of emitting a broad band with output from 400-1400 nm. The broad wavelength output is filtered, as stated above, by a few methods. Similar to laser systems, the choice of output wavelength should be determined by the target chromophore. The three primary chromophores are blood (oxy- and deoxy-hemoglobin), melanin in epidermal pigmented lesions and melanin in the hair shafts. Many systems have multiple, snap in filters which start at short wavelengths (Lumenis 515, 560, and 645 nm, etc.) and other systems use individual , specifically turned hand pieces, with dual filtration and produce more selective outputs (Palomar Medical

Technologies, Inc. StarLux-Lux V, 400-700nm and 870-1200 nm; Lux G 500-650 nm, and 870-1200 nm). These dual wavelength range hand pieces enable the user to more selectively target the desired chromophore. The choice of wavelength from an IPL device is a function of output of the xenon flashlamp (Figure 8) and the choice of wavelength filtration techniques relative to targeting the desired chromophore. Although many companies produce numerous "cut-off" filters, the real choice for improved selectivity for IPL technology is match the wavelength selectivity of the "cut-off" filters to maximize the absorption of the target chromophore (76).

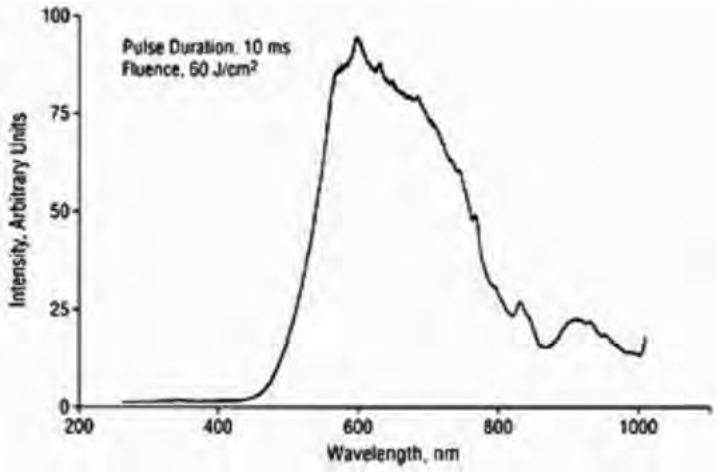


Figure 8. Emission spectrum of an intense pulsed light head with the 515 nm filter at 10-millisecond pulse duration. Peak output is shown by the line at 600 nm (54).

Specific hand pieces with the dual filtration process of improved selectivity can be applied to selective target such as vascular lesions. The 500-650 nm and 870-1200 nm dual wavelength range (Palomar StarLux Lux G hand piece) matched the primary absorption peaks of oxyhemoglobin (538 and 577 nm) with most of its output and then the remaining output matched the secondary absorption peaks near 900 nm. In addition, the long wavelength emission range begins to cover the absorption of water in the dermis (43).

The choice of wavelength range for targeting epidermal melanin is empirically easier because the absorption curve of is relatively linear. Melanin absorption is significantly higher in the shorter wavelength range (400 nm) than in the longer wavelength

range (1200 nm). In fact, the absorption coefficient is almost 15 times higher in the blue (400 nm) region of the spectrum than in the infrared (1200 nm) region of the spectrum. Therefore, when choosing a specific hand piece wavelength range or cut-off filter for targeting epidermal melanin, the shorter wavelengths are certainly more effective. The trade-off of wavelength choices is dependent on the amount of melanin present in the target relative to the amount of melanin present in the background skin. In other words, the ratio of melanin concentration of the primary target relative to the Fitzpatrick skin type of the individual will determine the choice of wavelength range to use as well as the treatment fluence (76). As with vascular lesions, if the skin type of the patient will tolerate shorter wavelengths well, the use of shorter wavelength, “blue” light will provide significantly higher selectivity for treating unwanted, epidermal pigmentation. Although lasers can provide excellent selectivity for treating epidermal pigmented lesions, the user is limited in choices by the very limited availability of short wavelength “blue” light systems. Therefore, for lasers, “green” wavelengths are most commonly used for treating pigmented lesions. As stated above, these “green” wavelengths (532 nm) are quite effective for treating vascular lesions and darker pigmented lesions, but are somewhat limited in treating lighter colored pigmented lesions. In this application area, IPL technology has a distinct advantage because the output wavelengths of the standard xenon lamps begin at 400 nm. Consequently, the IPL technology may actually provide more selectivity for treating pigmented lesions than laser technology (43).

- **Spot Size**

When treating blood vessels, spot size plays a very important role, because spot size, along with wavelength, affects penetration depth. A small spot size leads to rapid scatter with a rapid decay of fluence by depth. Penetration is therefore more efficient with a large spot size. A depth of 4 mm should be attainable with the 8 mm 35 mm rectangular spot size of the IPL device considering an average wavelength of 800 nm.

Larger spot sizes are always more effective in delivering light deeper into the skin and play an increasing important role especially for the use of IPL technology in treatment of large vascular lesions. The physical dimensions of the output waveguide surface area are very important in determining the effective fluence at the depth of the target (76).

However, IPL technology does present a different problem when considering the treatment of smaller, more superficial targets. Ectatic blood vessels are located in the upper dermis. Therefore, deep scattering into the reticular dermis is not necessarily a desirable output from a hand piece. Large are spot size hand pieces actually are disadvantage for treating linear or distinct vascular lesions and many pigmented lesions. The control or focusing of incoherent light is very different than that in laser light. As stated above, xenon flashlamps produce multiple wavelengths of light and because different wavelengths of light have different points, it is very difficult to focus accurately incoherent light. In other words, if one were to focus a laser beam, one would choose a lens that produced the appropriate spot size based on the wavelength of the laser and based on the fact that all of the laser light was coherent, directional, in-phase and monochromatic so a very small, tight spot could be produced. This is clearly how small spot size laser beams are produced for treating vascular lesions or for microspot treatments of small biological structures. However, this feature is impossible to duplicate with incoherent light (76). Being multiwavelength, multi-directional and incoherent, IPL light is difficult to focus. With the use of complex optical schemes, small spot size hand pieces have been designed (Palomar Medical Technologies, Inc Lux G and B hand pieces) for selectively treating vascular lesions. Spot sizes as small as 12 mm × 12 mm and 10 mm×15 mm can then produce fluences over 50J/ cm^2. At these fluences, even large vascular lesions can be effectively treated in one or two sessions. Therefore, spot size issues are multifaceted, depending largely on the choice of depth of the target. Larger spot sizes are most effective for delivering light to deep targets and small spot sizes are more effective

for delivering high fluences to more superficial targets(43).

- **Cooling**

Cooling of the epidermis during laser or IPL procedure is very important. Cooling can be divided into three areas, precooling, parallel cooling, and postcooling. Precooling and parallel cooling are generally the more important of the cooling processes. Cooling can be passive or active (contact or dynamic spray cryogen) in design and each has some advantages or disadvantages. The distinction between passive and active is very significant. Passive cooling has been employed in the past using ice-packs. Gels commonly are messy and very variable in their cooling capabilities. With the advent of active, pre- and parallel cooling on IPL systems, higher fluences and be employed and a large variety of skin types can be treated (56, 88).

Active contact cooling falls into numerous smaller categories, but the differences in the systems can be easily divided into two broader categories. First, the choice of waveguide materials is very important. Many technologies use quartz as the choice for the waveguide to carry the light pulse to the tissue. Quartz is an insulator and therefore a very poor thermal conductor. On the contrary, sapphire is the only crystalline material that has the same thermal conductivity properties of a metal. In other words, sapphire conducts heat from the surface of the skin in the same fashion as a piece of cold, opaque piece of metal. Secondly, the design of heat extraction from the waveguide is very important as well. The heat extraction rate is a function of the surface area in contact with the skin, the thickness of the sapphire of the waveguide and the heat transfer rate of the hand piece design. Because each flash of the IPL delivers significant thermal energy to the skin, the heat load of the skin and the rise in temperature of the waveguide all affect the temperature rise of the skin. If the hand piece is designed to minimize the temperature rise because if the hand pieces ability to remove a proportional amount of heat from the skin as the input heat load, then the system will effectively handle high fluence IPL treatments.

Human skin is actually a very good reflecting medium and because of this feature, a considerable amount of the input light from an IPL flash or laser pulse may be reflected or scattered from the skin. The ability to recapture this light and redirect it into the skin is a patented process termed "photon recycling" (55) and involves specific optical designs. Direct contact with the skin, the use of refractive index matching gels or lotions and the proper waveguide design all contribute to the success of minimizing photon leakage or scattering from the skin. It is not only reflection from the stratum corneum that matters, but also scattering from other structures throughout the epidermis and dermis that contribute to the total amount of input light normally lost with each light pulse. Photon recycling (especially on Fitzpatrick skin types I-III) may increase the effective fluence 2-3 times (43).

- **Pulse Durations**

Allowing proper thermal relaxation time between pulses theoretically prevents elevation of epidermal temperatures above 70^0 C and is an inherent advantage of "multiple sequential pulsing" of the IPL device. Thermal relaxation time is the amount of time it takes for the temperatures of a tissue to decrease by a factor of ε=2.72 (ε-expansion ratio) as a result of heat conductivity. For a typical epidermis thickness of 100 µm, thermal relaxation time is approximately 10 ms. For typical vessels 100 µm (0.1 mm), thermal relaxation time is approximately 4 ms, for a vessel of 300 µm (0.3 mm), thermal relaxation time is approximately 10 ms. Therefore, vessels > 0.3 mm cool more slowly than the epidermis with a single pulse. For larger vessels, however, multiple pulses may be advantageous with delay time of 10 ms or more between pulses for epidermal cooling. This delay time must be increased with larger vessels as thermal diffusion across a larger vessel elongates the thermal relaxation time. Multiple sequential pulsing with delay times permits successive heating of targeted vessels with adequate cooling time for the epidermis and surrounding structures (43).

These theoretical considerations implies: (1) vessels less than 0.3 mm should theo-

retically only require a single pulse, although a double pulse should have no adverse effect on treatment; (2) double or triple pulses should be spaced 10 ms or longer to accommodate normal epidermal thermal relaxation times, and that even safer might be at a 15 ms thermal relaxation time; (3) bright red lesions (oxyhemoglobulin) are better treated with 515-590 nm filters; (4) violaceous lesions (deoxyhemoglobulin) should be treated with the highest filter available accompanied by increasing delay times between pulses to allow for increased skin thermal relaxation times. The treatment of darker skin individuals becomes of increasing concern when performing photoepilation. In these cases, the 755 nm filter is used primarily with delay times between pulses from 50 to 100 ms to allow plenty of time for the skin to cool down avoiding thermal damage (76).

1.3.3.1.3. Side Effects from Light-Devices Treatment of Port Wine Stains

Treatment with light-devices is well tolerated, and the rate of persistent side-effects is rather low. Temporary side-effects comprise pain during treatment, swelling, erythema, purpura, blistering, crusts, transient hyperpigmentation or hypopigmentation, and skin infections. The most common persistent side-effects are scarring and permanent hyperpigmentation or hypopigmentation (78)

Unsuitable patients (because of skin type or suntan) are excluded from therapy. Irreversible pigmentary changes can be best prevented by adjusting wavelengths and fluences to a patient's skin type and treatment area and by using appropriate cooling devices. Scarring is rare and almost always evoked by overfluenced treatments or by crusting with subsequent manipulation and infection.

Bacterial and viral skin infections are among the recognized side-effects of laser treatment, probably as a consequence of a diminished skin barrier function after epidermal damage (79,80). Antimicrobial ointments may help to loosen the crusts and prevent bacterial infections. Although the PDL is rather selective for cutaneous blood vessels,

disruption of the epidermis does occur. Particularly individuals with a history of atopic eczema or recurrent herpes infections are at risk to develop such complications.

In general, the most important measure to prevent side- effects is the application of test shots for every chosen set of parameters and even for the same set of parameters applied at different parts of the body (78).

1.3.3.1.4. Limitations of the Laser Treatment of Port Wine Stains

Realistic information prior to treatment is extremely important. Patients should never be promised any type of success or least of all a total clearance of PWS (100). Many factors, such as size, color, localization, hypertrophy, or vessel architecture, influence the results of laser treatment (92- 95). After an average of 4–8 treatment sessions, PWS lighten up to ≥75% in around 40% of patients. A clearance rate of below 50% has been described in the literature in approximately 14–40% of all patients (92, 96). PWS located on the face respond better to laser therapy than those in non-facial localization, such as trunk and extremities (97-98). In a retrospective study on 874 patients with dermatomal facial PWS, PDL treatment produced unsatisfactory outcomes (84). PWS of the mandibular division of the trigeminal nerve responded best and those of the maxillary division responded worst. No significant difference was found between the color groups in response to treatment (85). PWS of the fingers and toes are difficult to treat because the skin is thicker in these areas (86), but results even vary within facial areas; for example, the central face tends to show less favorable results because of the thicker skin in this area (87). Furthermore, it has been demonstrated in an animal study that smaller blood vessels (Ø 2–16 µm) only showed incomplete photocoagulation(88). Thus, a high amount of very small vessels could lead to non-response of PWS.

Selective photothermolysis of PWS vessels requires two selective procedures: selective absorption of laser light in hemoglobin and selective vessel destruction using appropri-

ate pulse duration. Absorption of light in hemoglobin is described by the wavelength-dependent absorption coefficient. Due to the partially oxygenated hemoglobin in PWS vessels (~70%), the absorption coefficient is a composite of oxyhemoglobin and hemoglobin (89). When using appropriate wavelengths, only blood vessels are heated up to a certain temperature during laser irradiation. In addition, the energy of the laser pulse must be sufficiently high to exceed the coagulation threshold of blood vessels (temperature ≥70°C) (90). The heating-up process in the vessel is governed by the number of incoming photons per second, which is expressed by the optical peak power of the laser emission. PDL devices (585 nm, 0.45–1.5 ms) show good light absorption, for instance, 96% for large vessels of 200 μm, but only 15% for small vessels of 10 μm.

In the literature, different recurrence rates of PWS after completed laser treatment are reported. According to the study by Troilius et al. (91), 26% of patients suffered from recurring PWS after termination of PDL treatments (several months to 8 years). Other authors reported recurrence rates of 40–50% 2–4 years after PDL-treatment (82). Michel et al. (92) investigated the frequency of recurrence in 147 patients whose last PDL treatment was at least 1 year ago. In 24 patients (16.3%), partial redarkening was observed independent of the body site. Children under 10 years of age did not show any PWS recurrence, so that the age at the beginning of treatment may influence recurrence rates. A 10-year follow-up of 51 patients who had received PDL therapy of their PWS compared color measurements obtained before treatment, after completion of an average of five laser treatments of the complete PWS and a further session of a median of seven treatments. These authors observed significant redarkening of PWS at long-term follow-up, but it was still significantly lighter than it was when measured before any treatment (93). Finally, in a study by Hansen et al. (94), 19% of patients reported recurrence of color after 7 years of follow-up. Progressive ectasia, neovascularization resulting from thrombus formation, and angiogenesis from remaining parts of the stain may contribute to the long-term redarkening of PWS.

As has become evident, many different laser systems, incoherent light sources, as well as alternative treatment strategies have been investigated for the treatment of PWS. The PDL at a wavelength of 585–600 nm with variable pulse widths (ranging from 0.45 to 10 ms) in combination with epidermal cooling represents as a safe and effective treatment modality. Yet, other laser or light systems have also been reported to produce good clinical outcomes. Despite recent treatment advances, full clearance of PWS with the currently available lasers and incoherent light sources remains difficult. PWS show considerable clinical and histological heterogeneity, and a number of different approaches are likely to be needed for optimizing treatment. In contrast to laser, intense pulsed light (IPL) sources produce variable pulse durations as well as variable wavelength bands and, theoretically, the light emitted from an IPL system may therefore be matched to the absorption coefficient and thermal relaxation time of a broader range of PWS.

Thus it is of great interest to assess the efficacy and complications in the treatment of PWS using an IPL with broadband irradiation and long pulse durations.

HYPOTHESIS AND OBJECTIVES

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

On the base of the previously exposed data and considering the most contemporary knowledge of anatomy and pathophysiology of the port wine stains and the possibilities of the light devices for treatment of vascular lesions, we aimed to investigate the abilities of intense pulse light in the clinical treatment of port wine stains.

We established the following hypothesis:

1. The intense pulsed light treatment could be the first line treatment of port wine stains because of its high efficacy and safety profile.

2. The clinical results of intense pulsed light treatment of port wine stains are related with the anatomical location, color and size of the lesions and patient's age.

3. The recurrence rate after successful treatment of port wine stains with intense pulsed light depends on patient's age at the beginning of the treatment course.

2.2 Objectives

In order to test the hypothesis we set the following objectives:

1. To review and describe the intense pulsed light procedures in treatment of port wine stains during the last seven years.

2. To evaluate the efficacy (clearance rate) of intense pulsed light treatment of port wine stains according to the characteristics of the lesions (anatomical location, color and size) and the age of patients.

3. To check if there is any relation between the recurrence rate of the port wine stains treated with intense pulsed light and the age of the patients at the beginning of the treatment course.

MATERIALS AND METHODS

Contents

3. MATERIALS AND METHODS

In this work a retrospective descriptive study was conducted based on the revision of the clinical data and photo documentation of the patients with vascular anomalies treated with different light devices. The patients were treated between November 2008 and July 2015 at the Department of Dermatology of Military Medical Academy in Sofia, Bulgaria. All the treatments were performed by the same team with the main investigator of the present study being the head of the team. When necessary, a plastic surgeon, pediatrician and neurologist were attracted as consultants. All the photographs were taken with the same device under the same conditions (light, distance, position). A minimal follow-up of 12 months after the last procedure was selected for the design of the study.

3.1. Patients included in the study

A total of 149 patients with PWS with different anatomical locations treated with IPL were explored for their possible inclusion in the study. As an exclusion criteria were selected: pregnancy, breast feeding, the intake of retinoids or photosensitizing medications, diseases or genetic conditions causing photosensitivity or tending to aggravate after light exposure, any previous treatments (3 patients), and uncompleted follow-up (2 patients) Thus a total of 144 patients were included. Of them 68 (47.2%) were male and 76 (52.8%) female. The distribution of the patients by sex is depicted on Table 6 and Table 8.

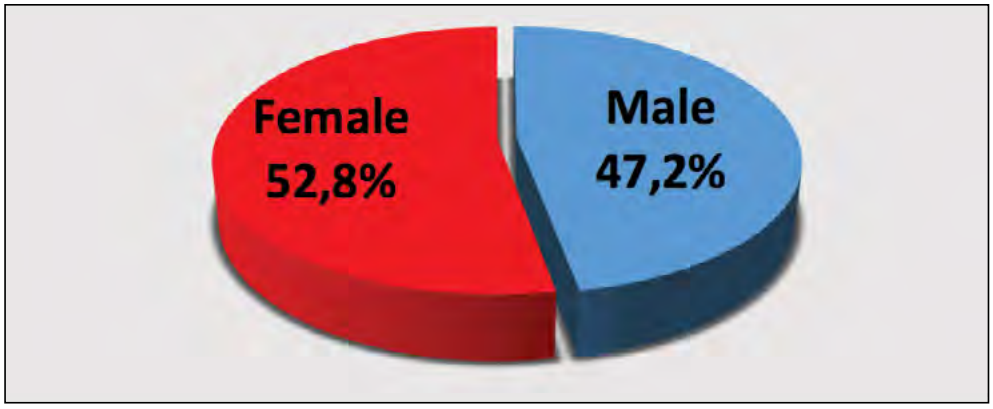


Table 6. Distribution of the patients of the study by sex.

The age of the patients at the time of the first treatment varies from 8 months to 47 years (mean age 31.4 years). The distribution of the patients by age is shown on Tables 7 and 8.

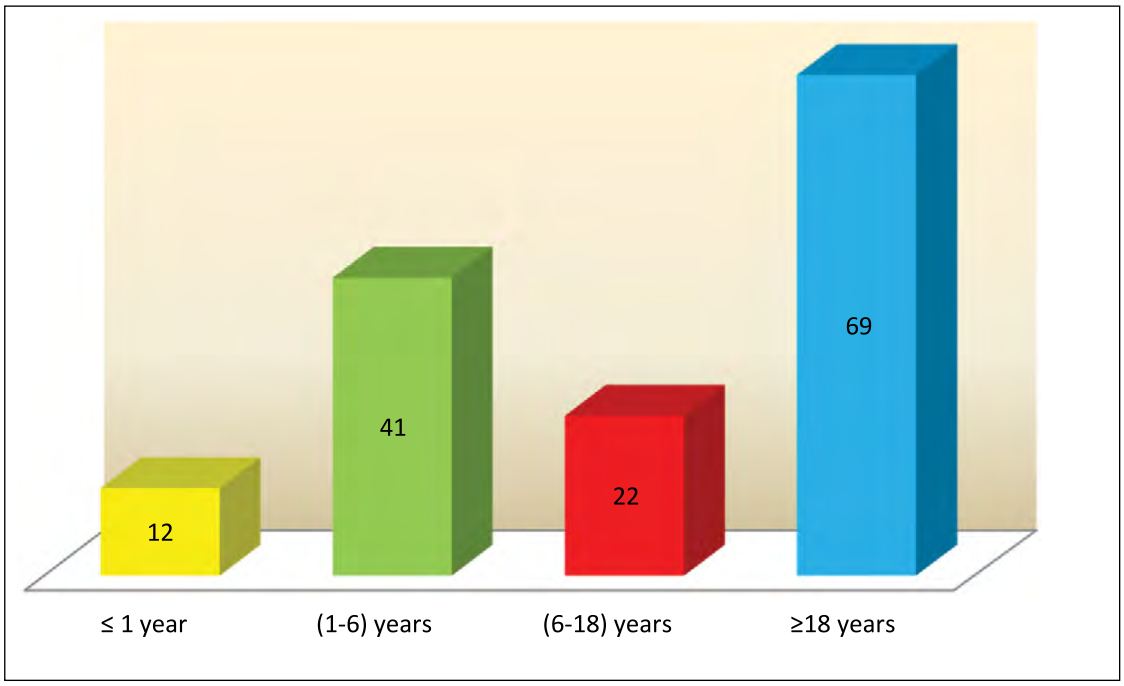


Table 7. Distribution of the patients in the study by age at the time of the first treatment.

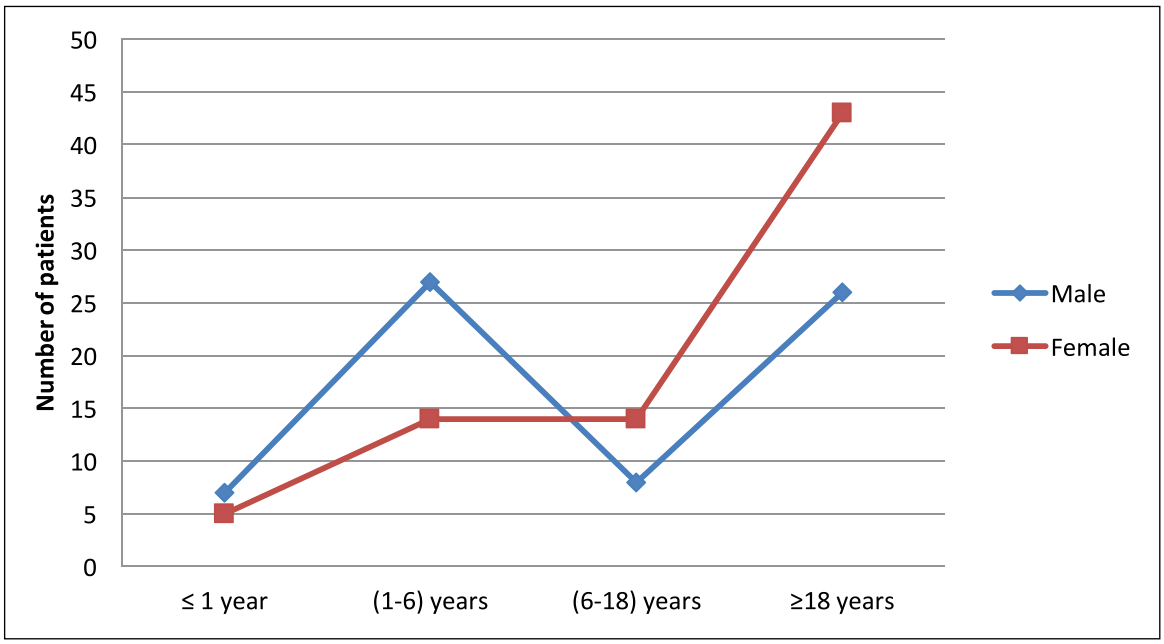


Table 8. Distribution of the patients by sex and age at the time of the first treatment.

From practical point of view the patients under age 18 were included in a different group with corresponding subdivision into 3 subgroups presented in Table 9.

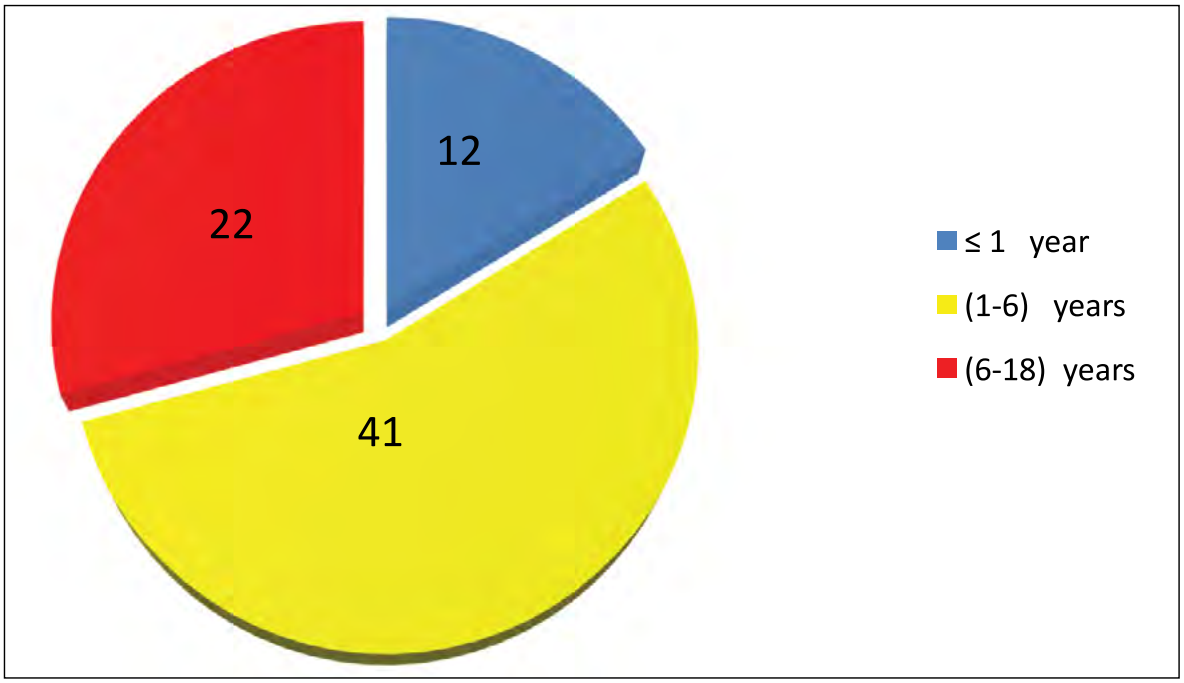


Table 9. Distribution of the patients under 18 year-old.

3.2. Characteristics of lesions

Taking into account that PWS may have different clinical expression(95) and location, in order to make any future analysis, we divided the patients in 3 different groups according to the color of lesions: pink, red and thickening (Table 10). Another important issue of practical point of view is the location of the lesions on the body area. Considering that we divided the patients into 3 groups: with affection of the head, affection of the neck and affection of the trunk and extremities (Table 11).

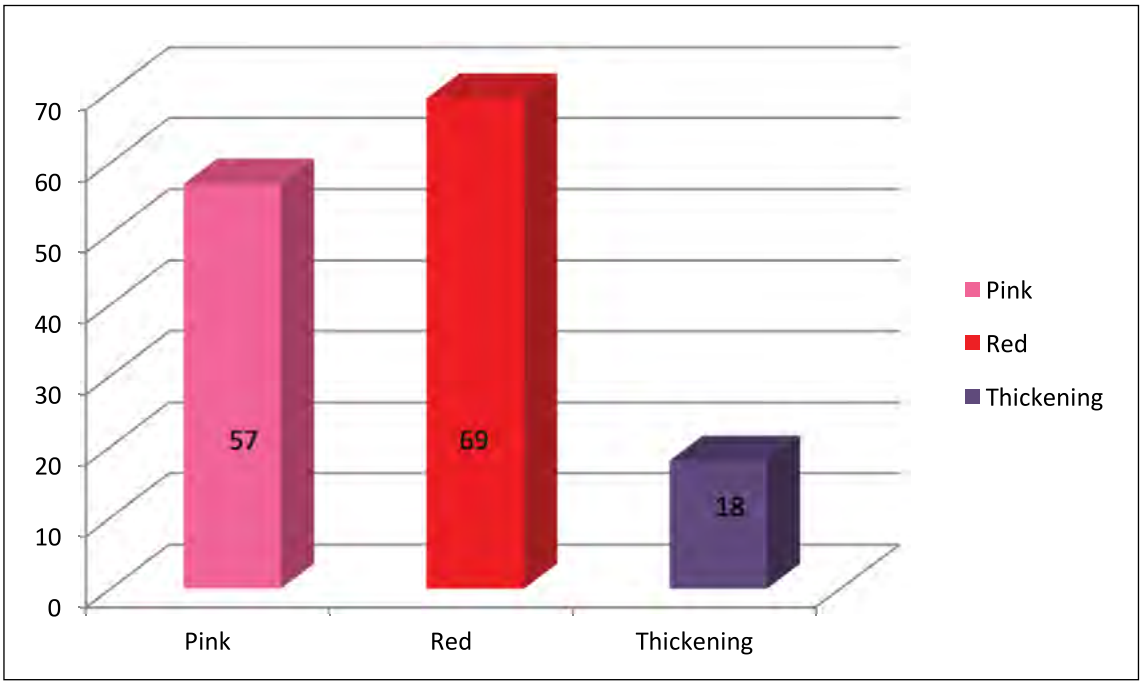


Table 10. Distribution of the patient by the characteristics of the lesions.

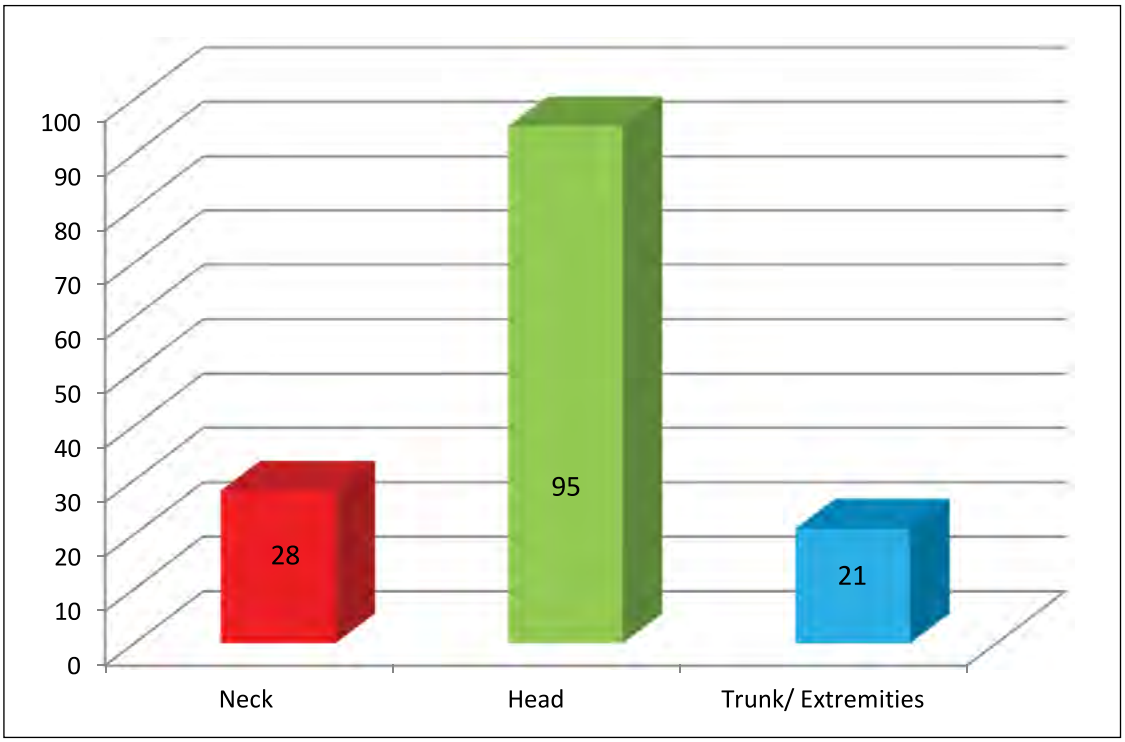


Table 11. Locations of the lesions on the body.

3.3. Patient evaluation

Before the initiation of the treatment course all patients were evaluated according to Fitzpatrick classification of the skin type (Table 12):

Skin type	Typical Features	Tanning ability
I	Pale white skin, blue/green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Table 12. Fitzpatrick's Classification of skin types.

A special attention was paid in 2 cases suspicious for Sturge-Weber syndrome where this syndrome was clinically excluded by a combined team consisting of neurologist, pediatrician, and dermatologist. A hypertrophic scar formation due to any traumatic process or previous surgeries were not detected on physical examination and patient's history in all the patients.

All patients received an initial consultation, and were given enough information both verbally and written about the treatment protocol and the adverse reactions.

All patients signed an informed consent form before the first procedure. For the patients under age of 18 the consent was signed by their parents.

3.4. Practical aspects step by step

The first step in patient's treatment is the clear and unequivocal diagnosis of the entity to be treated. Patients were provided with both verbal and written information on the planned IPL treatment, the chance of success, all potential side-effects, and alternative treatment options. A signed informed consent was mandatory, describing therapy sequelae, such as pain, blistering, purpura, or crusting, and potential side-effects, such as erythema, hypopigmentation, hyperpigmentation, atrophy, scarring, hypertrophic scarring, or keloid formation, as well as the risk of infection.

The skin type of every patient was documented according to Fitzpatrick scale and the photo-physical parameters were adjusted according to individual patient's skin type. Patients had not to be tanned and were instructed to avoid sunlight for 6–8 weeks after laser treatment or, at least, use sufficient UV protection (58) (Figure 9). Such protection is important as the melanin content of the epidermal layer is a competing absorber of the emitted light (96).

Figure 9. Sun protection with 50SPF used after IPL treatments.a

Photo documentation was mandatory prior to each single treatment, at one month, at six months and at 12 months after the last procedure. As reactive erythema develops over several minutes after laser treatment, PWS edges is to be treated first or the lesion's borders should be outlined. Eye protection with appropriate goggles was used. The treatment of upper and

lower eyelids required the insertion of steel eye shields (Figure 10) or sterile rubberized contact lenses. A prediction of which wavelength enables the best lightening is only possible after the application of test shots with light device available. Depending on the particular light device, overlapping of spots may be necessary to compensate the Gaussian beam profile (97).

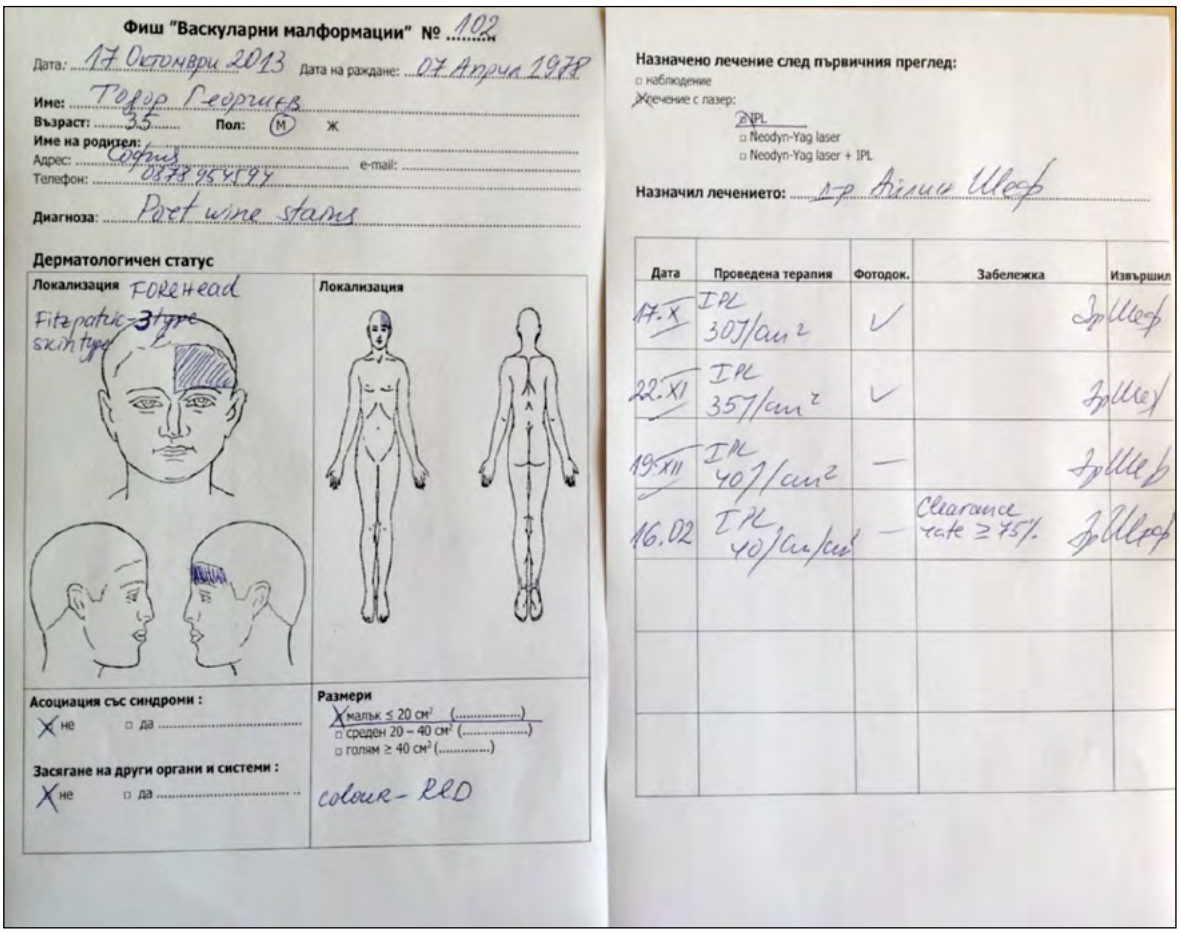
Figure 10. Steel extra- and intra-ocular eyeshields which were used during IPL treatments.

All patient's data such as demographics, skin type, characteristics of port wine stains including color and location, treatments parameters, percentage of clearing, and treatment complications were recorded and entered into a database specially designed for this survey (Figure 11).

An almost constant side-effect of IPL treatment is the sense of pain during treatment. For adults, pain does not present such a severe problem; however, children or patients susceptible to pain or with larger lesions may require repeated treatment breaks or general anesthesia. The use of EMLA cream in infants younger than 3 months is associated with an increased risk of developing methemoglobinemia as a result of immature erythrocyte methemoglobin reductase (97). Furthermore, EMLA cream may blanch pale lesions, making them more difficult to view during treatment. General anesthesia also influences lesional blood flow. The deeper the level of sedation during general anesthesia, the lighter is the PWS lesion. This problem may be overcome by placing patients with a head or neck PWS in an exaggerated Trendelenburg position to fill the dilated capillaries (98).

Most light devices are equipped with cooling devices that effectively cool the skin surface and reduce pain during treatment. Cryogen spray cooling protects the epidermis during laser therapy while leaving dermal structures susceptible to thermal damage.

After the treatment, the patient has to stay out of the sun or at least use sufficient UV protection for the following 8 weeks. Retreatment is conducted after 4–6 weeks. Depending on the success of the treatment, multiple sessions may be necessary.



Фиш "Васкуларни малформации" № 102

Дата: 17 Октомври 2013 Дата на раждане: 07 Април 1978

Име: Тодор Георгиев

Възраст: 35 Пол: (М) Ж

Име на родител:

Адрес: София e-mail:

Телефон: 0879954792

Диагноза: Port wine stains

Дерматологичен статус

Локализация Forehead

Fitzpatrik skin type 3

Локализация

Асоциация със синдроми :

X не □ да

Засягане на други органи и системи :

X не □ да

Размери

X малък ≤ 20 см² (.....)

□ среден 20 – 40 см² (.....)

□ голям ≥ 40 см² (.....)

colour - RED

Назначено лечение след първичния преглед:

□ наблюдение

X лечение с лазер:

X IPL

□ Neodyn-Yag laser

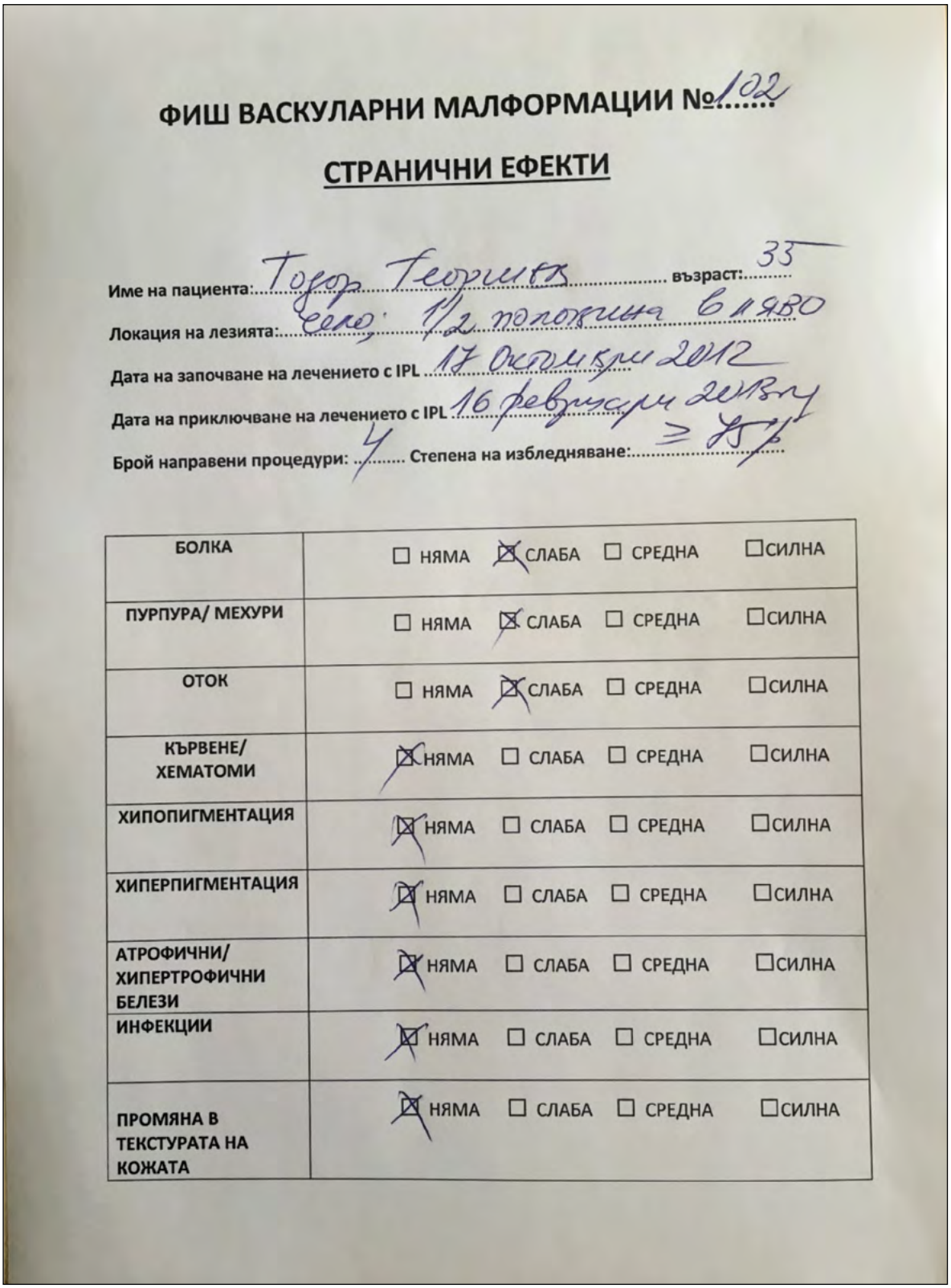
□ Neodyn-Yag laser + IPL

Назначил лечението: д-р Айлин Шеф

Дата	Проведена терапия	Фотодок.	Забележка	Извършил
17.X	IPL 30J/cm²	V		д-р Шеф
22.XI	IPL 35J/cm²	V		д-р Шеф
19.XII	IPL 40J/cm²	–		д-р Шеф
16.02	IPL 40J/cm²	–	Clearance rate ≥ 75%.	д-р Шеф

Figure 11. Patient data record which was especially designed for the survey.

(A) General.



ФИШ ВАСКУЛАРНИ МАЛФОРМАЦИИ №102

СТРАНИЧНИ ЕФЕКТИ

Име на пациента: Тодор Георгиев възраст: 33

Локация на лезията: ляво: 1/2 положна 6 ляво

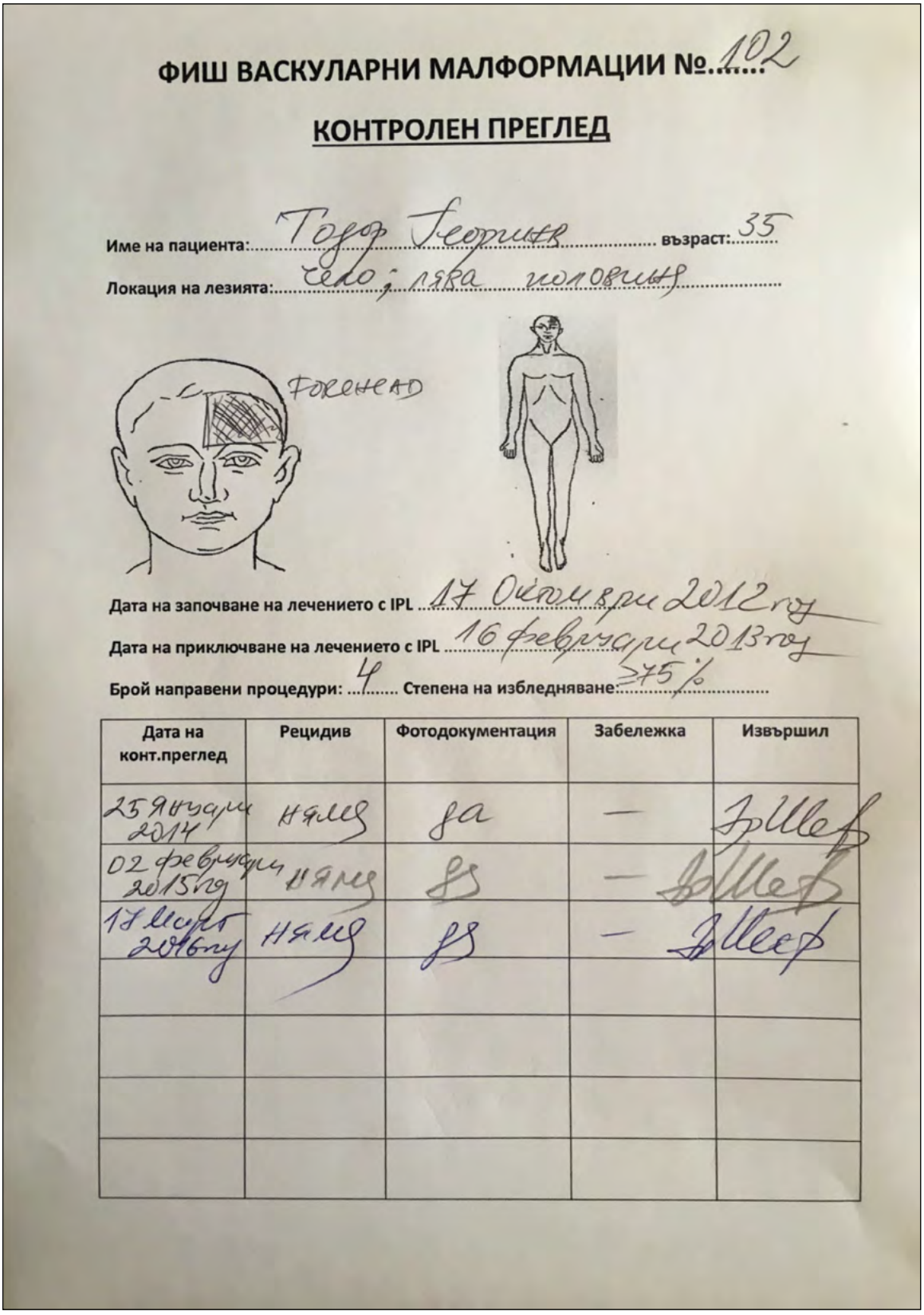
Дата на започване на лечението с IPL 17 октомври 2012

Дата на приключване на лечението с IPL 16 февруари 2013 г.

Брой направени процедури: 4 Степена на избледняване: ≥ 75%

БОЛКА	☐ НЯМА	☒ СЛАБА	☐ СРЕДНА	☐ СИЛНА
ПУРПУРА/ МЕХУРИ	☐ НЯМА	☒ СЛАБА	☐ СРЕДНА	☐ СИЛНА
ОТОК	☐ НЯМА	☒ СЛАБА	☐ СРЕДНА	☐ СИЛНА
КЪРВЕНЕ/ ХЕМАТОМИ	☒ НЯМА	☐ СЛАБА	☐ СРЕДНА	☐ СИЛНА
ХИПОПИГМЕНТАЦИЯ	☒ НЯМА	☐ СЛАБА	☐ СРЕДНА	☐ СИЛНА
ХИПЕРПИГМЕНТАЦИЯ	☒ НЯМА	☐ СЛАБА	☐ СРЕДНА	☐ СИЛНА
АТРОФИЧНИ/ ХИПЕРТРОФИЧНИ БЕЛЕЗИ	☒ НЯМА	☐ СЛАБА	☐ СРЕДНА	☐ СИЛНА
ИНФЕКЦИИ	☒ НЯМА	☐ СЛАБА	☐ СРЕДНА	☐ СИЛНА
ПРОМЯНА В ТЕКСТУРАТА НА КОЖАТА	☒ НЯМА	☐ СЛАБА	☐ СРЕДНА	☐ СИЛНА

Figure 11. Patient data record which was especially designed for the survey (Cont'd): (B) Side effects.



ФИШ ВАСКУЛАРНИ МАЛФОРМАЦИИ №..102

КОНТРОЛЕН ПРЕГЛЕД

Име на пациента: Тодор Георгиев възраст: 35

Локация на лезията: чело; лява половина

FOREHEAD

Дата на започване на лечението с IPL 17 Октомври 2012год

Дата на приключване на лечението с IPL 16 февруари 2013год

Брой направени процедури: 4 Степена на избледняване: >75%

Дата на конт.преглед	Рецидив	Фотодокументация	Забележка	Извършил
23 Януари 2014	няма	да	—	Шеф
02 февруари 2015год	няма	да	—	Шеф
17 март 2016год	няма	да	—	Шеф

Figure 11. Patient data record which was especially designed for the survey (Cont'd): (C) Follow up visits.

3.4.1. IPL system

- **Lux G handpiece**

The patients in our study were all treated using the Lux G handpiece (Figure 12). The LuxG handpiece is a novel intense pulsed light system (IPL) with optical spectral wavelength filtering for versatility. Developed as an accessory to the StarLux Pulsed Light & Laser System platform (© Palomar Medical Technologies, Inc., Burlington, MA, USA), the LuxG delivers dual-band spectral output in the 500 nm to 670 nm region and in the 870 nm to 1400 nm region. The spot size of the handpiece is 15×10 mm and the maximum fluence is 70 J/cm^2. Active contact cooling of the handpiece minimizes the risk of side effects and improves patient comfort during treatment. The treatment intervals were 4 to 6 weeks for three to six treatments sessions.

Figure 12. Palomar Starlux 500 and Lux G handpiece.

3.4.2. Treatment parameters

Typically, treated sites received two passes. The first pass was performed with a longer pulse duration (10-20 ms depending on the vessel diameter and depth) and the second pass was performed using a shorter pulse duration (5-10 ms). Fluences ranged from 30 J/cm^2 to 50 J/cm^2 depending on the pulse duration. If end-point reactions such as transient

grayness or blanching of the blood vessels and/or general erythema of the area were not observed, the fluence was increased 2J/cm^2 on a neighboring area. Finally, the whole lesion was treated at the fluence in which the endpoint reactions were seen (Figure 13).

Figure 13. Patient with PWS on the neck before (A) and after (B) the end of the IPL treatment. At the Figure B the end-point reaction as transient grayness is depicted.

This fluence was fixed or increased in following sessions. In addition, the number of pulses and the delay between pulses were increased in order to obtain optimal response.

Before each treatment, the area was cleaned and a cool colorless ultrasound gel of approximately 2 to 3 mm thickness was applied before each shot to protect the epidermis from thermal injury and to aid in delivering the light uniformly onto the treated area. The crystal light guide was placed parallel to the skin over the treatment area without pressure in order to avoid expelling blood from the PWS (Figure

14). Every light spot adjoined each other without overlapping.

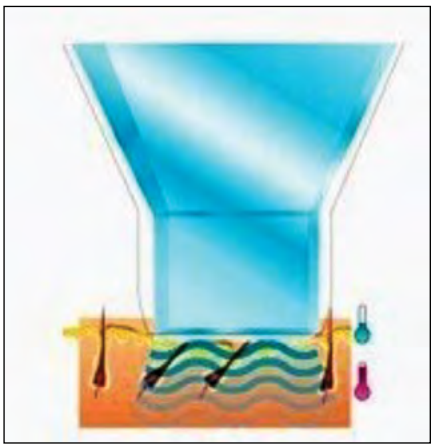


Figure 14. Active cooling system of Lux G handpiece parallel to the skin over the treatment area.

After the treatment, cold compresses and ice pacts (Figure 15) were used for 20 minutes and an antibiotic ointment (Figure 16) was applied to treat area without the use of systemic medication. A topical anesthetic cream was not applied to patients in the first session. However, some of them needed an anesthetic cream due to burning and/or pain sensations in the following sessions. Following the treatment, an after-sun cream was applied to the treated areas to help protect the skin. The patients were advised to continue with this 4 to 6 hourly for the first few days following treatment. They were all advised to use highest factor sunscreen and to protect the treated area from exposure to excessive sunlight for the duration of the trial.

Figure 15. Ultrasound colorless gel and icepacks that are used for the IPL treatments.

The endpoint for treatment of each patient was taken to be when no further fading was noted in the treatment area, despite increasing the fluence and varying the pulse train and pulse delay. The patient and the doctor jointly took this decision to cease the treatment. Photographic records were kept on all patients. The presence and absence of scarring, hypopigmentation, hyperpigmentation, and recurrence were noted at each visit throughout the study period. Patients were informed that purpura and mild edema was considered to be a normal post-treatment reaction and were not recorded as adverse events. Applying the IPL on the lesion was performed by the same clinician. Short- and long-term side effects and percentage of fading in the treated areas was evaluated by other doctors.

Figure 16. Antibiotic ointment applied after procedure.

3.5. Efficacy evaluation

Treatment efficacy was evaluated according to the photographic analysis. Each pre- and postoperative photograph was subjected to evaluation by computerized, triple objective comparative assessment of color shading with use of the program Skin Lesion Color Change (SLCC) created by Pawel Szychta (99). Patient responses were divided into four groups according to the clearance rate of the lesion: excellent- 75-100% clearing; good- 50-75% clearing; fair- 25-50% clearing; poor- less than 25% clearing (Table 13) (100). The response rate was determined via the following formula:

(cases of excellent + cases of good + cases of fair) / total cases

Clinical effect was evaluated with photographs 6 and 12 months after the last treatment.

Excellent response	75-100% clearing
Good response	50-75% clearing
Fair response	25-50% clearing
Poor response	<25 % clearing

Table 13. Treatment response of PWS after laser procedure.

The following side effects were evaluated at the 6-month follow-up: hypopigmentation, hyperpigmentation, atrophic scarring and hypertrophic scaring. All side effects were evaluated on the following scale: none, slight, moderate and severe.

3.5.1. Photo documentation system

All photographic documentation was performed with Canon POWERSHOT G3X digital camera (© Canon Inc., China) (Figure 17) before and after each treatment and at the follow-up visits in order to compare efficacy. All photographs were taken in jpeg format and standardized in terms of magnification, lighting and positioning.

Figure 17. Canon POWERSHOT G3X digital camera.

3.6. Statistical analysis

Data were analyzed using the chi-squared test or Fisher's exact probability. A **chi-squared test**, also referred to as a **test** (or **chi-square test**) (Figure 18), is any statistical hypothesis test where in the sampling distribution of the test statistic is a chi-square distribution when the null hypothesis is true. Chi-squared tests are often constructed from a sum of squared errors, or through the sample variance. Test statistics that follow a chi-squared distribution arise from an assumption of independent normally distributed data, which is valid in many cases due to the central limit theorem. A chi-squared test can be used to attempt rejection of the null hypothesis that the data are independent (101).

Also considered a chi-square test is a test in which this is *asymptotically* true, meaning that the sampling distribution (if the null hypothesis is true) can be made to approximate a chi-square distribution as closely as desired by making the sample size large enough. The chi-squared test is used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories (102).

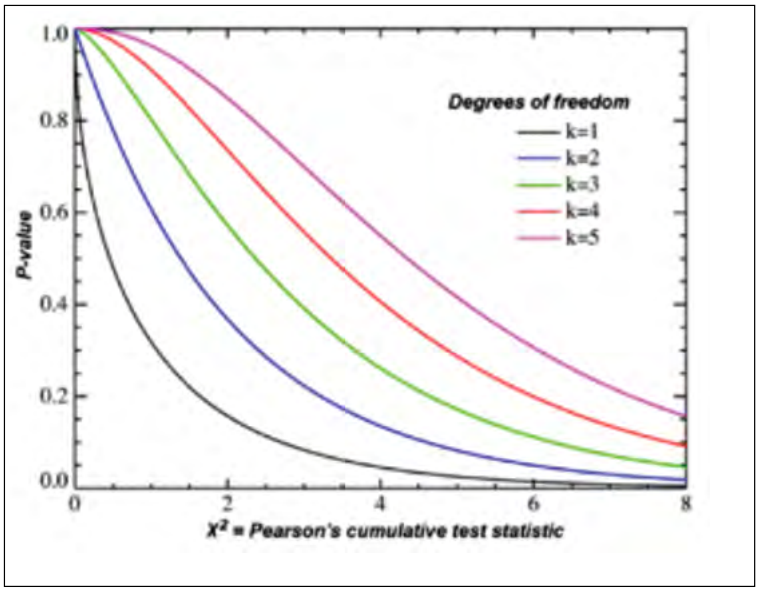


Figure 18. Chi-square distribution, showing X^2 on the x-axis and P-value on the y-axis.

Fisher's exact test (114-116) is a statistical significance test used in the analysis of contingency tables. Although in practice it is employed when sample sizes are small, it is valid for all sample sizes. It is named after its inventor, Ronald Fisher, and is one

of a class of exact tests, so called because the significance of the deviation from a null hypothesis (e.g., P-value) can be calculated exactly, rather than relying on an approximation that becomes exact in the limit as the sample size grows to infinity, as with many statistical tests. The test is useful for categorical data that result from classifying objects in two different ways; it is used to examine the significance of the association (contingency) between the two kinds of classification. Most uses of the Fisher test involve a 2 × 2 contingency table. The p-value from the test is computed as if the margins of the table are fixed and will therefore provide guesses with the correct number in each category. As pointed out by Fisher, this leads under a null hypothesis of independence to a hypergeometric distribution of the numbers in the cells of the table.

With large samples, a chi-squared test can be used in this situation. However, the significance value it provides is only an approximation, because the sampling distribution of the test statistic that is calculated is only approximately equal to the theoretical chi-squared distribution. The approximation is inadequate when sample sizes are small, or the data are very unequally distributed among the cells of the table, resulting in the cell counts predicted on the null hypothesis (the "expected values") being low. The usual rule of thumb for deciding whether the chi-squared approximation is good enough is that the chi-squared test is not suitable when the expected values in any of the cells of a contingency table are below 5, or below 10 when there is only one degree of freedom (this rule is now known to be overly conservative (104)). In fact, for small, sparse, or unbalanced data, the exact and asymptotic p-values can be quite different and may lead to opposite conclusions concerning the hypothesis of interest (118,119). In contrast the Fisher exact test is, as its name states, exact as long as the experimental procedure keeps the row and column totals fixed, and it can therefore be used regardless of the sample characteristics. It becomes difficult to calculate with large samples or well-balanced tables, but these are exactly the conditions where the chi-squared test is appropriate.

For hand calculations, the test is only feasible in the case of a 2 × 2 contingency table. However the principle of the test can be extended to the general case of an m × n table (106), and some statistical packages provide a calculation (sometimes using a Monte Carlo method to obtain an approximation) for the more general case (107).

RESULTS AND DISCUSSION

4. RESULTS AND DISCUSSION

There were 76 (52.8%) female and 68 (47.2%) male patients among our 144 patients. Their ages ranged from 8 months to 47 years. Seventy five were children under 18 years old and 69 were adults older than 18 years. In the group of children there were 33 female and 42 male and in the group of adults there were 43 female and 26 male. Sixty seven patients (47%) had Fitzpatrick skin type III, 48 (33%) patients had Fitzpatrick skin type IV and 29 (20%) patients with skin type II (Table 15).

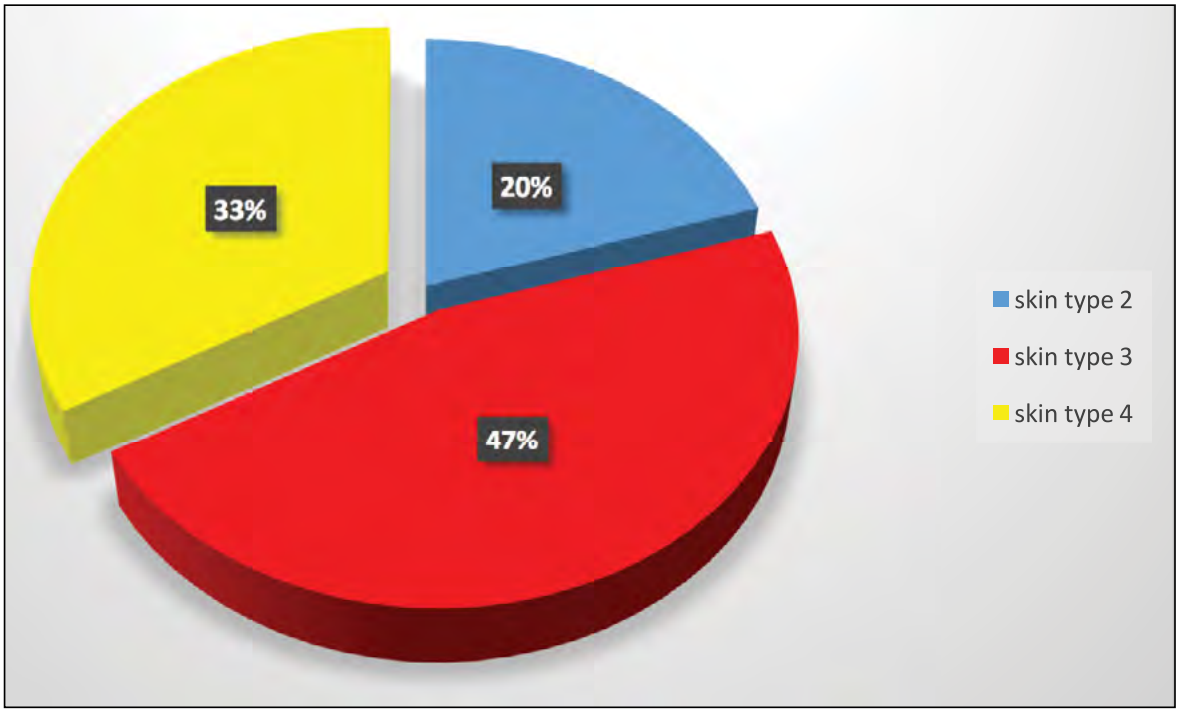


Table 15. Distribution of the patients by Fitzpatrick skin type.

The vascular lesions in our study were located in 3 locations: 95 (65.97%) on the head, 28 (19.45%) on the neck and 21(14.58%) on the trunk and extremities. Location of PWS on the head was separated into four categories: (i) 14 forehead (14.74%), (ii) 41 peripheral face (43.16%), (iii) 28 central face (29.47%) and (iiii) 12 mixed (12.63%) (Figure 19).

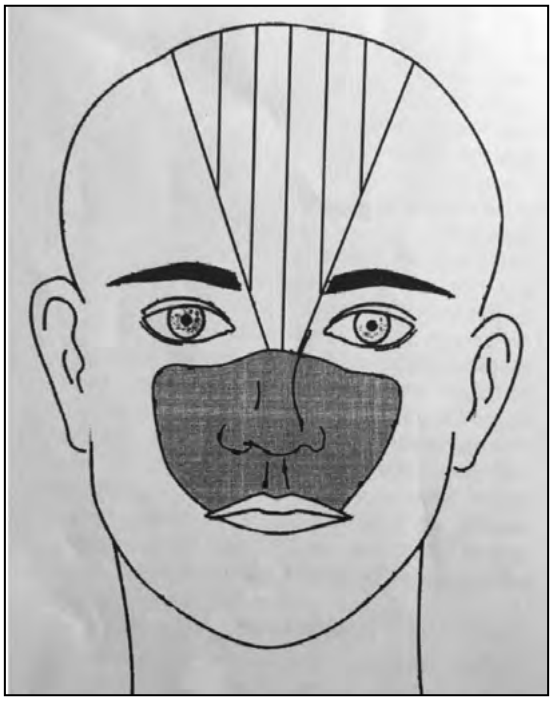


Figure 19. The lined area represents the central forehead. The shaded area represents the central face. All other area were considered peripheral (108)**.a**

According to color and thickness, all the lesions were divided into three types: (i) 57 pink -39.58%; (ii) 69 red- 47.92%; and (ii) 18 thickening-12.50%. Whereas 43 (29.9%) patients had five or less than five consecutive treatment sessions, 46 (31.9%) patients had from 5 to 10 treatment sessions, and 55 (38.2%) had more than 10 treatment sessions (Table 14).

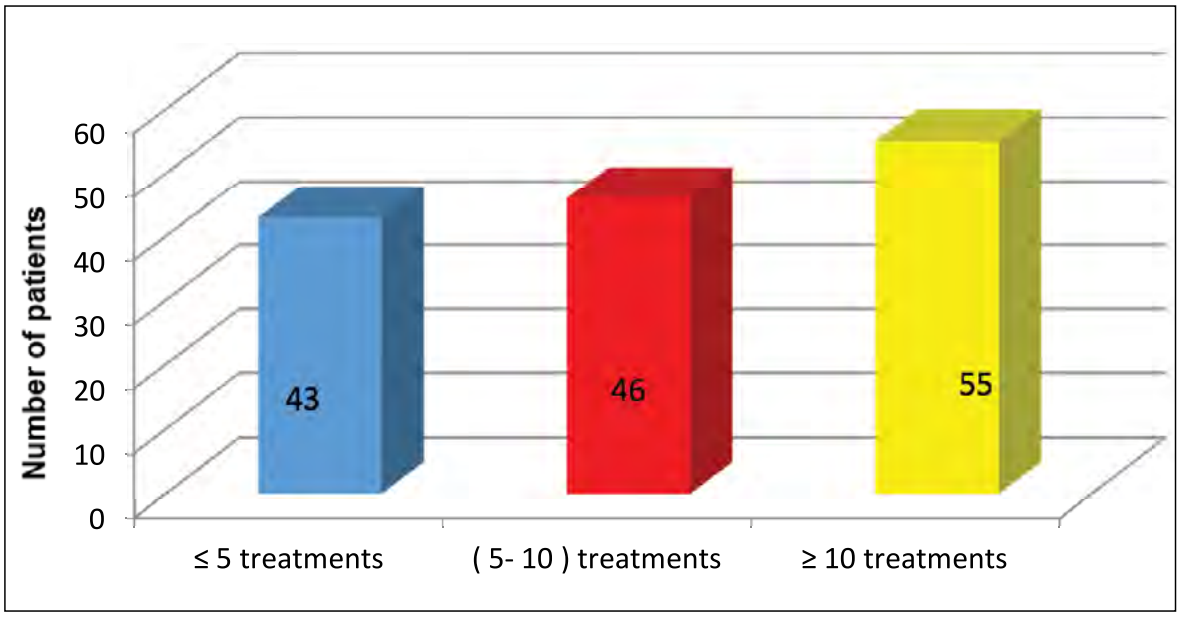


Table 14. Number of treatments that patients in the study completed.

4.1. Efficacy of Treatment

4.1.1. Efficacy and size of PWS

To examine the relation between PWS size and the treatment efficacy, the patients were placed into three groups according to the size of their PWS: (i) less than 20 cm^2 where we have found 92 patients (67%), (ii) 20-40 cm^2 with 35 patients in the group (24%) and (iii) 40 cm^2 or more where 17 patients (12%) were found (Table 16).

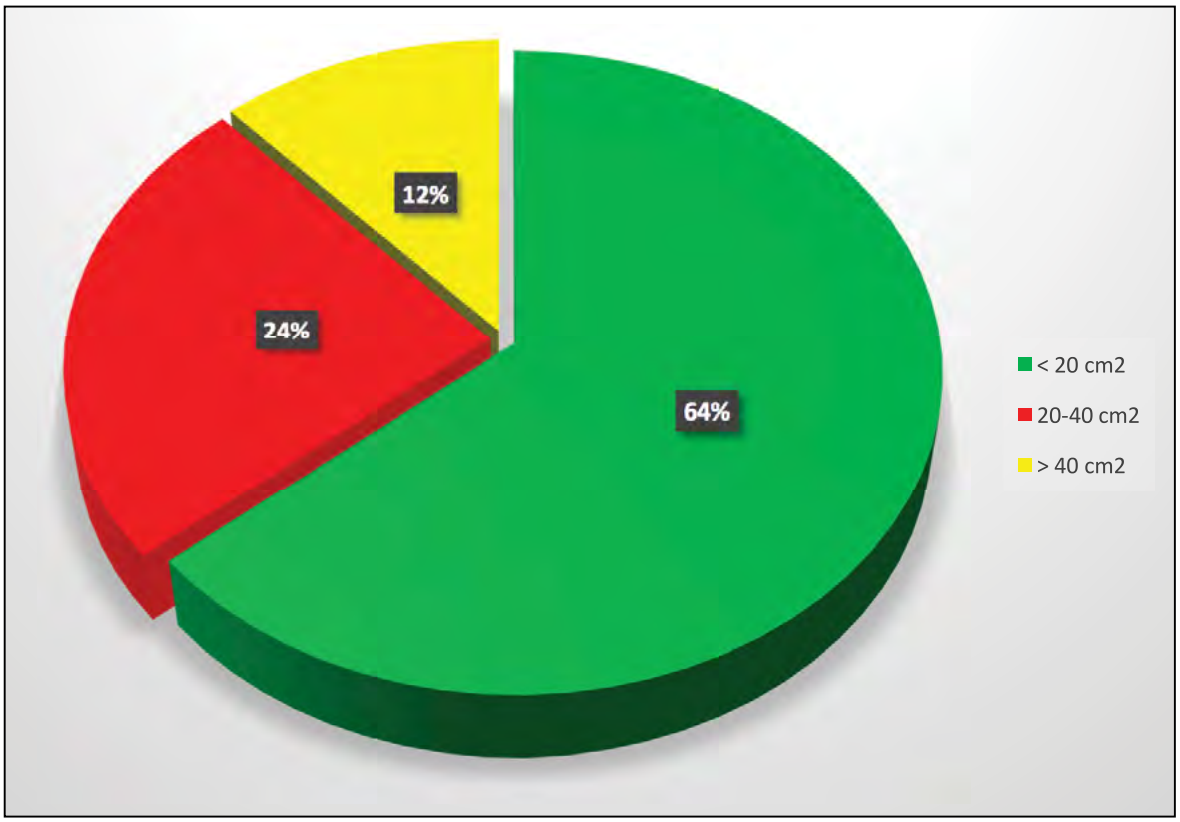


Table 16. Distribution of the patients by size of the lesion.

Fisher's Exact Test was applied and analysis showed a significant statistical association ($p<0,001$) between clearance rate and the size of the treated port wine stain (Table 17). In this table it is showed that lesions less than 20 cm^2 had the best response to IPL. In this group 23 (25%) of 92 lesions had more than 75% clearance rate, this result is not seen in the other two groups. When decreases the clearance

rate, this trend is reversed, highest frequency has the group of lesions with size 40 cm^2 or over. For lesions with size 20-40 cm^2, the biggest group of 20 (57.1%) PWSs were with clearance rate between 25%-50%. In the group of patients with lesions bigger than 40 cm^2, there were not even one patient with clearance rate more than 50%. Seven (41.2%) of these patients had less than 25% clearing. When a lesion is very large (40 cm^2 or more), the mean decrease in size is initially poor, but response to subsequent treatments is steady.

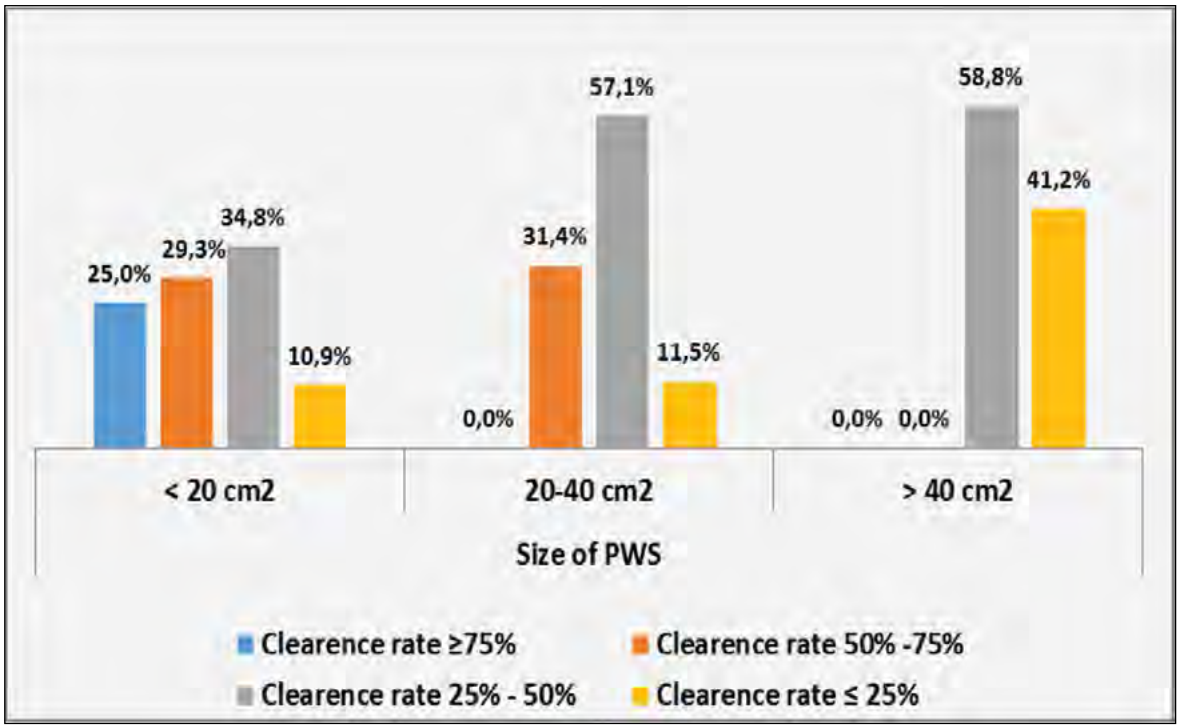


Table 17. Clearance rate and size of PWS.

A previous study conducted by Nguyen et al (108) examined the effect of PWS size on the treatment with pulsed dye (585nm) laser (PDL). Regarding response as a result of size, the average decrease in size was best for the smaller PWSs. Lesions under 20 cm^2 had the best result after treatment and cleared 67% after the first 5 treatments, then 21% after the second 5 treatments, followed by lesions 20 to under 40 cm^2 (45%, 8%), and lesions more than 40 cm^2 (23%, 29%). The lesions more than 40 cm^2 had a small decrease in size initially but steadily responded with more treatments. In gen-

eral, these findings coincide with ours although the cited study by Nguyen and team was conducted by using PDL.

In another study of Yohn JJ (109), 74 adult patients with facial, truncal, and extremity port-wine stains (PWS) were treated with the flashlamp-pumped pulsed dye laser (PDL) with laser output ranging from 6.0 to 7.5 J/ cm^2. Response to treatment was analyzed by comparing the area of involvement following each treatment with the area of involvement measured in the first treatment session. All the PWS responded with 25% to 90% lightening, and 85.1 percent of patients achieved 25 percent clearing. However, only 36.5 percent achieved 50 percent clearing, and none of the patients achieved 100 percent clearing. None of four patients with PWS greater than 100 cm^2 achieved 50 percent clearing following a mean of 17.2 +/- 5.7 treatments. Adult patients need to be made aware that complete clearing may not be obtainable by PDL treatment alone. This is especially important for adult patients with PWS larger than 100 cm^2 who cleared not completely compared to patients with small lesions.

A 1995 study by Morelli et al.(110) evaluated the importance of age and lesion size regarding the effect of pulsed dye lasers (PDL) treatment on facial PWSs in children. Children younger than 1 year showed the highest percentage of clearing (mean 65.41%). Children aged 1 to 2 years had a mean clearing of 61.67%, children older than 2 years to 6 years had a mean clearing of 54.06%, children older than 6 years to 12 years had a mean clearing of 49.29%, and children older than 12 years to 18 years had a mean clearing of 58.02%. The rate of clearing decreased as age increased. Most patients with lesions clearing 75% or 100% were younger than 1 year. Differences in clearing rates between groups were not caused by number of treatments and the size effect is apparent at all ages.

In the terms of size, 15 of the 47 patients with PWSs under 20 cm^2 had 100% clearing, whereas 3 of the 36 patients with PWSs more than 20 cm^2 had lesions that totally cleared. Lesions under 20 cm^2 showed a mean clearing of 60.52%, lesions

between 20 and 40 cm^2 showed a mean clearing of 61.5%, and lesions more than 40 cm^2 showed a mean clearing of 41.41%.Overall, 18 patients had 100% clearing of their lesions. Smaller lesions cleared better than larger lesions at all ages. Researchers acknowledged size and patient age must be considered before starting PWS treatment. As in the 1991 study of Ashinoff and Geronemus (111), researchers recommended PDL treatment for PWSs as early as possible.

The results from our survey confirmed that port wine stains with smaller size have better response to IPL treatments than bigger ones (Figure 20 and Figure 21)

Figure 20. A woman with PWS on the cheek with size less than 20 cm^2 before (A) and 12 months after (B) two IPL treatments-more than 75% clearance rate.

However we were unable to find any study on the relation discussed above on the IPL treatment of PWS to compare because all the previous surveys on importance of the size of the lesions and their response to treatment were done with PDL.

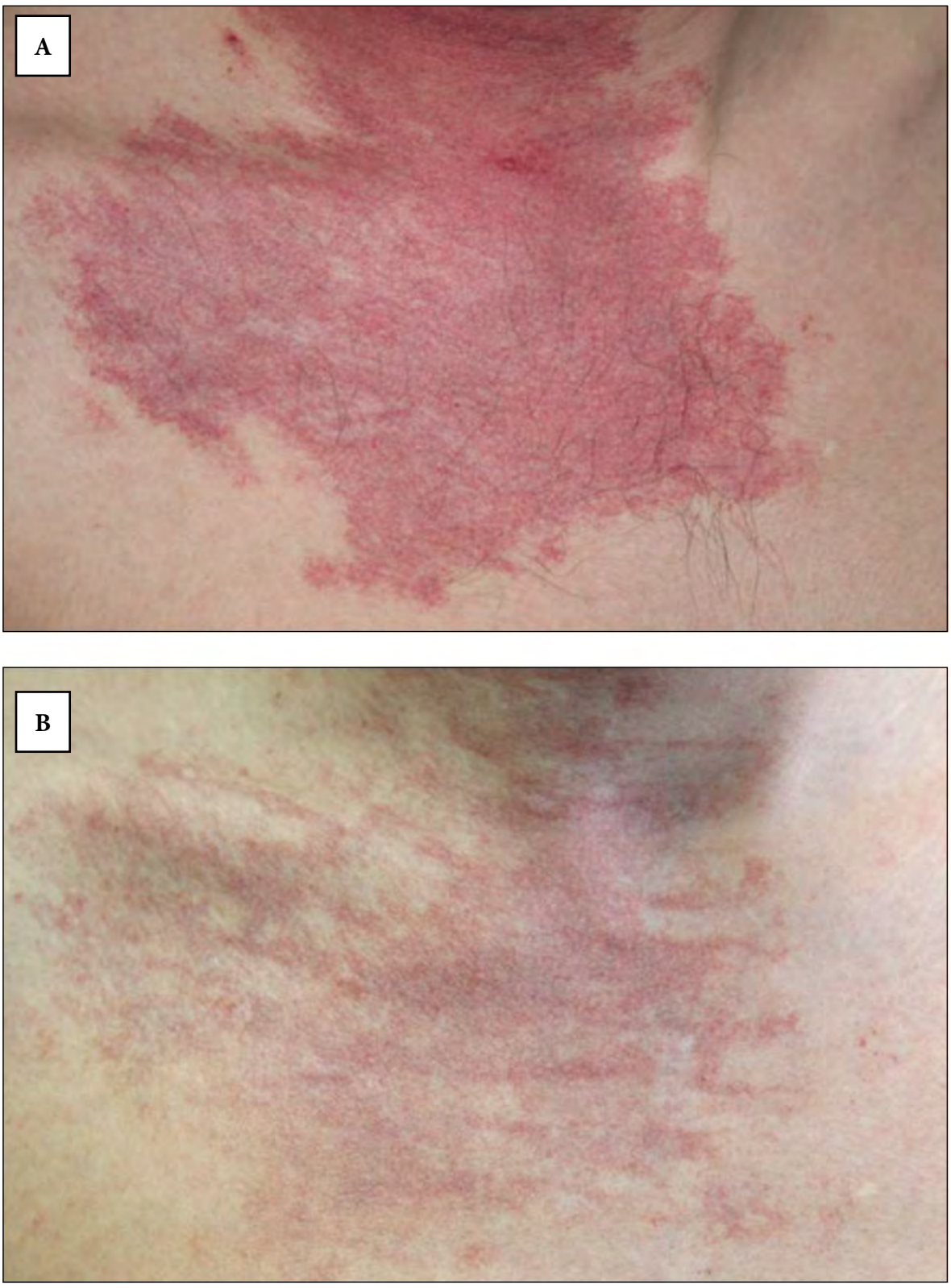


Figure 21. Patient with port wine stain on the chest with size 20-40 cm2 before (A) and after (B) four IPL treatments- 50% clearance rate.

4.1.2. Efficacy in adults versus children

In our survey we examined whether the age of treated patients affects their response to IPL procedures. There were 69 (47.92%) adults, e.g. patients older than 18 years, and seventy-five (52.08%) children, e.g. patients younger than 18 years who were treated (Table 18).

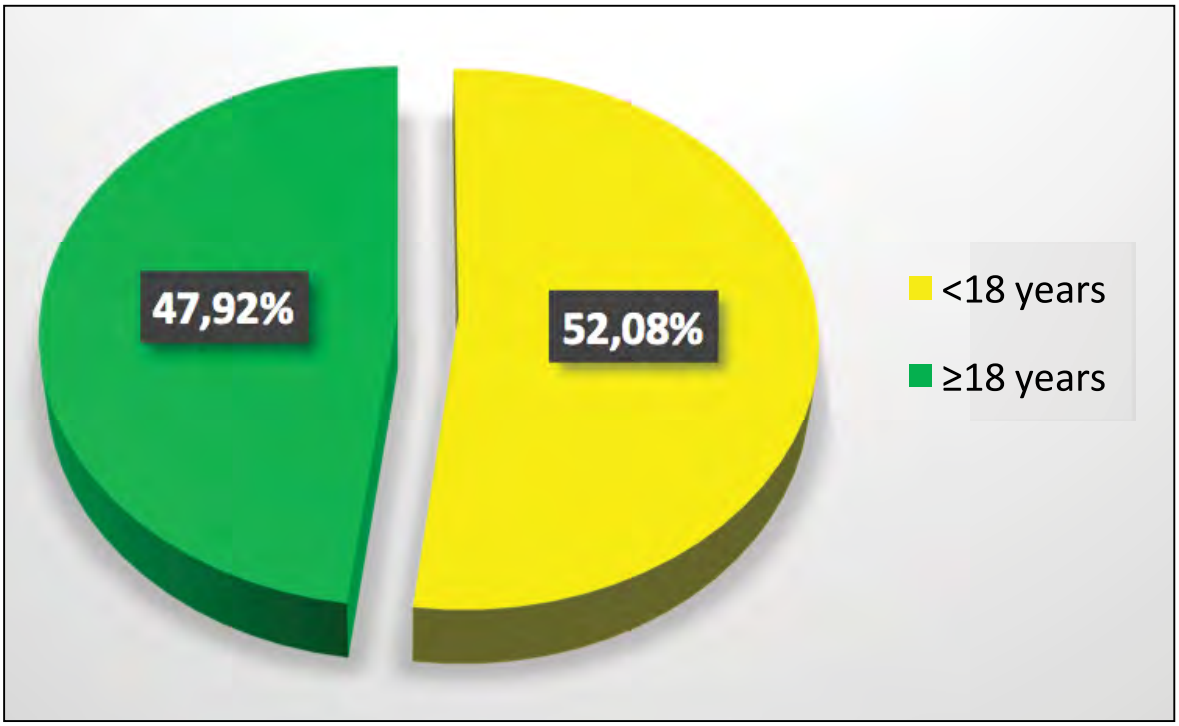


Table 18. Distribution of patients by age.a

We found that there is statistically significant association between the age of the patients and the clearance rate after IPL treatments (Table 19).

Clearance rate		Age				Total	p-value
		≤ 1	(1-6)	(6-18)	≥18		
≥75%	N	7	5	5	6	23	<0,001
	%	58,3%	12,2%	22,7%	8,7%	16,0%	
50% -75%	N	4	18	6	10	38	
	%	33,3%	43,9%	27,3%	14,5%	26,4%	
25%- 50%	N	1	8	9	44	62	
	%	8,4%	19,5%	40,9%	63,8%	43,1%	
≤ 25%	N	0	10	2	9	21	
	%	0,0%	24,4%	9,1%	13,0%	14,5%	
Total	N	12	41	22	69	144	
	%	100,0%	100,0%	100,0%	100,0%	100,0%	

Table 19. Age of the patients and clearance rate.

We stated that in children group (younger than 18 years) there was bigger clearance rate compared to the adults. The clearance rate more than 75% in the youngest group (younger than 1 year) is seen in 58.3% (7/12) of all the treated patients, whereas in the adult group (older than 18 years) is only 8.7% (6/69). Clearance rate from 50% to 75% was highest in the group of children 1 to 6 years- 43.9% (18/41). Half of patients (11/22) at ages between 6 to 18 years had a clearance rate more than 50%. In the group of adults (older than 18years) 63.8% (44/69) of them had 25%-50% lightening. These findings of our study showed that the clearance rate decreases with the increase of the patient's age (Figure 22).

Figure 22. A 2-year old patient with PWS before (A) and after (B) two IPL treatments.

In 1990, Reyes and Geronemus (61) observed the effect of the PDL on PWSs in 73 children between the age of 3 months and 14 years and found out that younger patients responded significantly better than older patients. The 44 of 73 (60%) patients between

3 months and 6 years old showed 55% lightening after one treatment, whereas the 29 of 73 (40%) older patients had 48% lightening after one treatment.

It has been hypothesized by Morelli et al (110) that children with their thinner skin and smaller sized PWS should need fewer treatments with the PDL than adults. The percentage of children achieving complete clearance of their PWS is considerably less than initially reported by Reyes et al. (61). More than 75% lightening was achieved with an average of 2.5 treatments in 33 patients (45%), 50% to 74% lightening after an average of 1.7 treatments in 31 (42%), 26% to 49% lightening after 2 treatments in 5 (7%), and less than 25% lightening after 1 treatment in 4 (5%). The overall average lightening after one treatment was 53%. The percentage of lightening increased as the number of treatments increased. Three patients had 100% clearance of the port-wine stain. Patients aged between 3 months and 6 years (44 patients) had a better response after the first treatment (55% lightening) than did patients aged between 7 and 14 years.

Better results with early treatment were reported by Tan et al (112) in their study of 35 children, 3 months to 14 years of age, with disfiguring port-wine stains when treated with a flashlamp-pulsed tunable dye laser. All had complete clearance of the stains after an average of 6.5 laser treatments to each lesional area; skin over bony prominences required approximately half as many sessions as skin on the cheek. Children less than seven years old required fewer sessions (mean +/- SD, 5.8 +/- 1.1) than older children (7.1 +/- 1.1; P less than 0.05).

In Alster's study (113) infants and younger children did not need significantly fewer treatment in comparison to older children (older than 8 years of age) and adults. These studies were all retrospective, and none used objective measurements to assess the results. Van der Horst et al (114) investigated in a prospective study 100 patients with PWS (age of 0-31 years). They were treated with PDL and the treatment result was judged with the help of a colorimeter. They found no evidence that PDL treatments is more effective in early childhood than at later age.

Contrary to the others, Guang Li et al (95) reported that the efficacy in adults was found to be better than in children. They assumed that possible reasons to this may be that during treatment, no anesthesia was used, even when treating children, which may have limited the total treatment; or that PWS vessels of children with PWS may be smaller than those of adults, and thus the vessels of a child would respond less to the IPL; and the study's limited cases were not enough to achieve an unprejudiced results.

It has been shown that younger patients have vessels that are smaller in diameter and are less full of erythrocytes (115). This may help to explain the good response to IPL treatment seen in patients less than 1 year old in our series as well as in others cited above. The mean decrease in color for the first five treatments for ages 1-6 years, however, is the same as for the older age group (over 6 years) (Figure 23). One explanation is that this younger group of children grows rapidly. Enlargement of a PWS during growth of the child will partially offset the decrease in size gained from treatment.

Treatment during early childhood is desirable in order to reduce the psychologic impact of a cosmetically significant congenital malformation (117,130,131).

Figure 23. A 4-year old patient with PWS before (A) and after (B) three IPL treatments.

In the present study we evaluated the association between the number of treatments needed to achieve maximum clearance rate and the age of the patients. The patients were divided

into three groups: (i) less than 5 treatments, (ii) from 5 to 10 treatments and (iii) more than 10 treatments. Fisher's Exact Test was applied and found statistical significance ($p<0.001$) between the number of treatments and the age of the patients in the group of children younger than 1 year and in the group of adults (Table 20).

Number of treatments		Age	
		≤ 1	≥18
≤ 5	N	9	1
	%	75,0%	1,4%
(5- 10)	N	3	18
	%	25,0%	26,1%
≥ 10	N	0	50
	%	0,0%	72,5%
Total	N	12	69
	%	100,0%	100,0%

Table 20. Relation between number of treatments and the age of patients.

In this table it is distinctly seen that 75% (9/12) of children under the age of 1 needed 5 or less treatments to achieve best results (more than 75% lightening) and none of them needed more than 10 treatments. On the contrary, in the group of adults 1.4% (1/69) needed 5 or less procedures and 72.5% (50/69) needed more than 10 procedures. This result is presented graphically on Table 21.

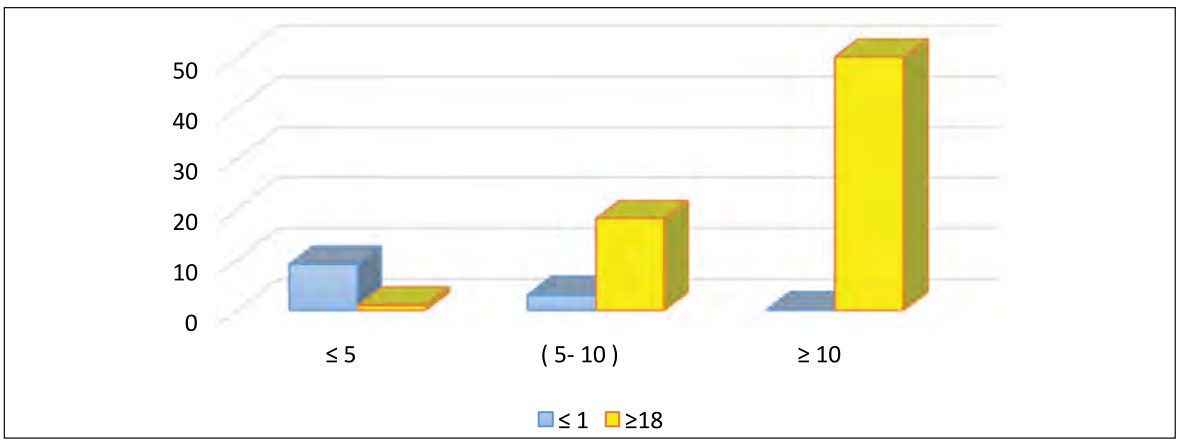


Table 21. Relation between number of treatments and the age of patients.

Thus, our results showed that with the increase of the age of the patients the number of treatment sessions also increased.

Several studies of pulsed dye laser treatments for PWS during infancy indicate that more rapid clearing is possible with less number of procedures. In a study of 35 children, 3 months to 14 years of age, Tan et al (118) found that children less than 7 years old required fewer laser treatments sessions than older children for PWS clearing. Another study of 73 children between the age of 3 months and 6 years showed increased clearing of their lesions after one laser treatment compared to children between 7 and 14 years of age (119). Pulsed dye laser treatment of PWS in 83 children produced complete clearing in 32% of those who began treatment before 1 year of age compared to 18% of those treated after 1 year of age (120). A study of 133 children and adults found the highest percentage of good and excellent clearing in those patients who were 0-10 years during treatment (121). Alster and Wilson reported 87% lesional clearance in patients less than 2 years and 73% in patients 16 years and older (113). In contrast, a study by Van der Horst et al (114) found no difference in treatment results between age groups. The validity of this study is questionable because only partial treatment of PWS lesions was performed during each treatment session, and treatment intervals were excessively long (114). The greater success of pulsed dye laser treatment in infants and young children can be attributed to decreased skin thickness, permitting better laser penetration, smaller vessel diameter, and smaller lesional surface area. Successful treatment is possible in adults with hypertrophic lesions, but they may require a higher number of treatment sessions. These findings are relevant to ours given although the applied device is PDL. It could be speculated that IPL, being in fact a multiple laser device, could achieve the same result and our results confirm that.

4.1.3. Efficacy in different clinical types of PWS

One hundred forty-four patients in our study were divided into three types according to their clinical manifestation: (i) 57 pink (39.58%); (ii) 69 red (47.92%); and (iii) 18 thickening (12.50%) (Table 10). In the group of pink lesions 89% (51/57) of patients were younger than 18 years and 11% (6/57) were older than 18 years (Table 22).

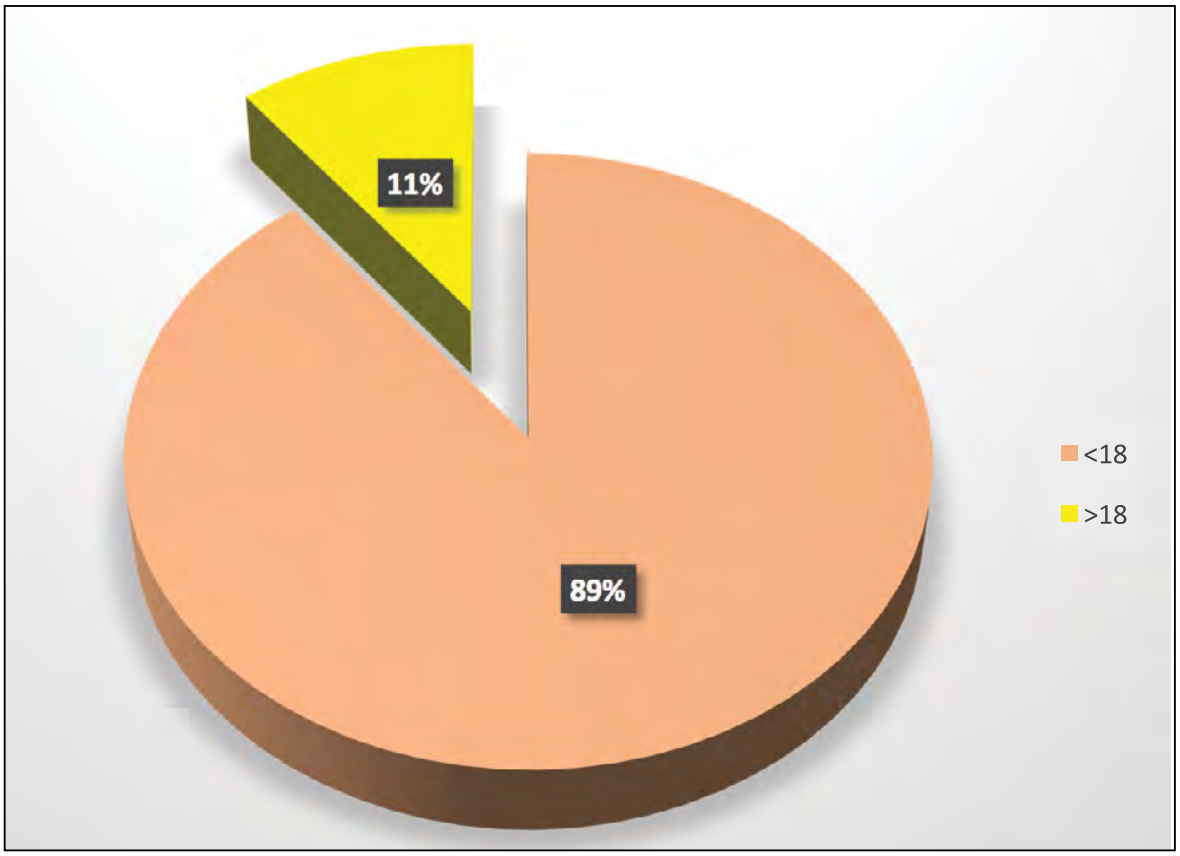


Table 22. Distribution of pink lesions by the age of the patients.

Sixty five percent (45/69) of patients with red lesions were adults and 35% (24/69) were children (Table 23). There were no children in the group with thickening lesions (Table 24).

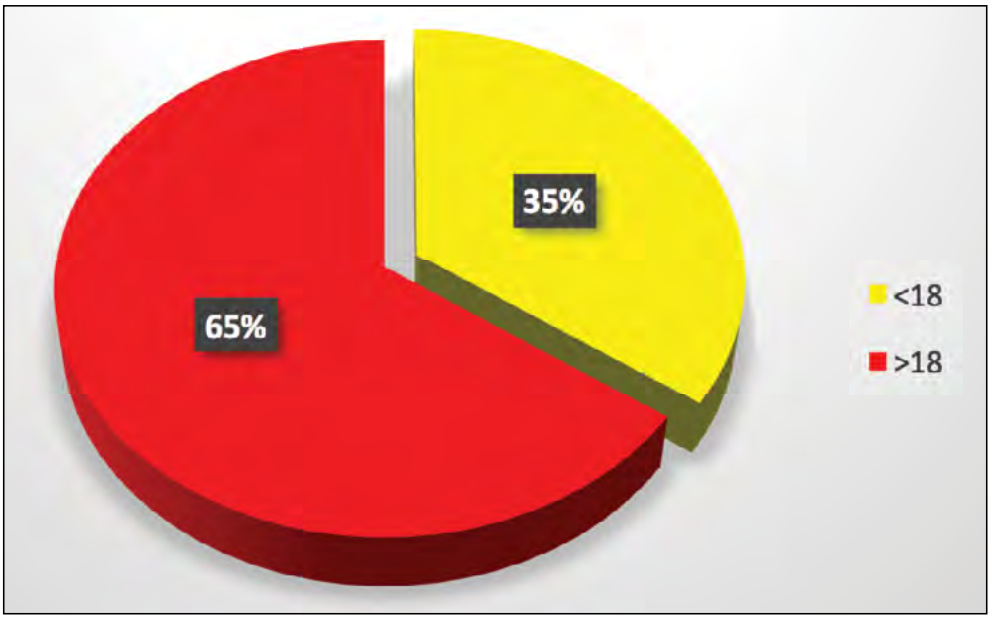


Table 23. Distribution of red lesions by the age of the patients.

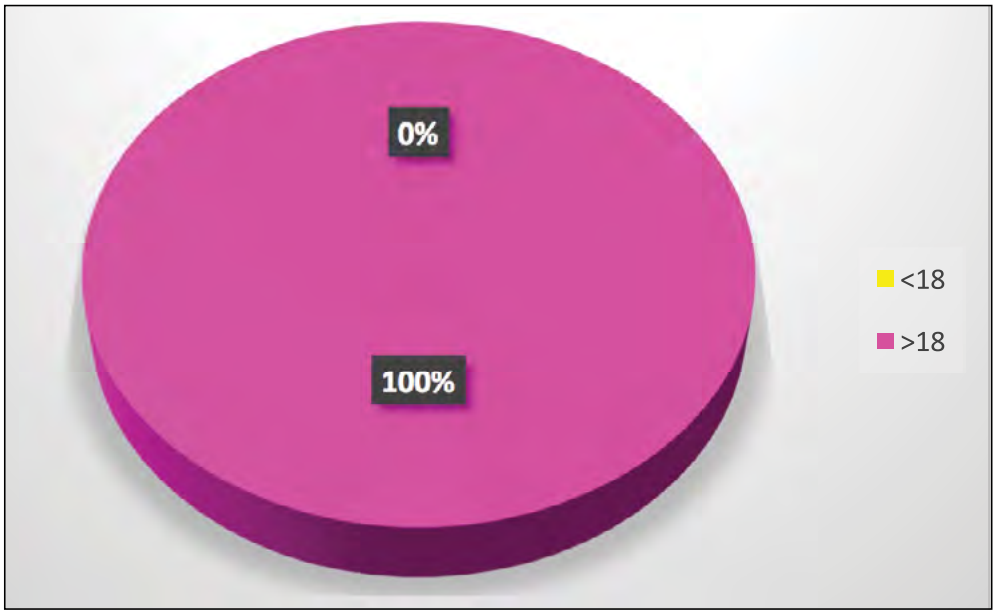


Table 24. Distribution of thickening lesions by the age of the patients.

The color of PWS lesions is determined by the diameter and depth of the blood vessels within the dermis. Usually, vessels in pink lesions are deeper in the skin and smaller in diameter, while vessels of a purple lesion are deeper in the skin and bigger in diameter, and vessels of red lesions are usually shallower in the skin (122). As our study was a retrospective one, we have no data on the diameter and depth of blood vessels for the different lesions treated. We divided the lesions into three types simply according to color and hyperplasia, which was easy to judge in clinical applications.

To increase efficacy of IPL treatments reasonable parameters have to be selected according to the different lesions types. For the pink lesions, longer wavelength light filters and shorter pulses and energy between 40 to 50 J can be selected. For the purple thickening lesions, shorter wavelength light filters and longer pulses and higher energy more than 50J may be preferred (Table 25).

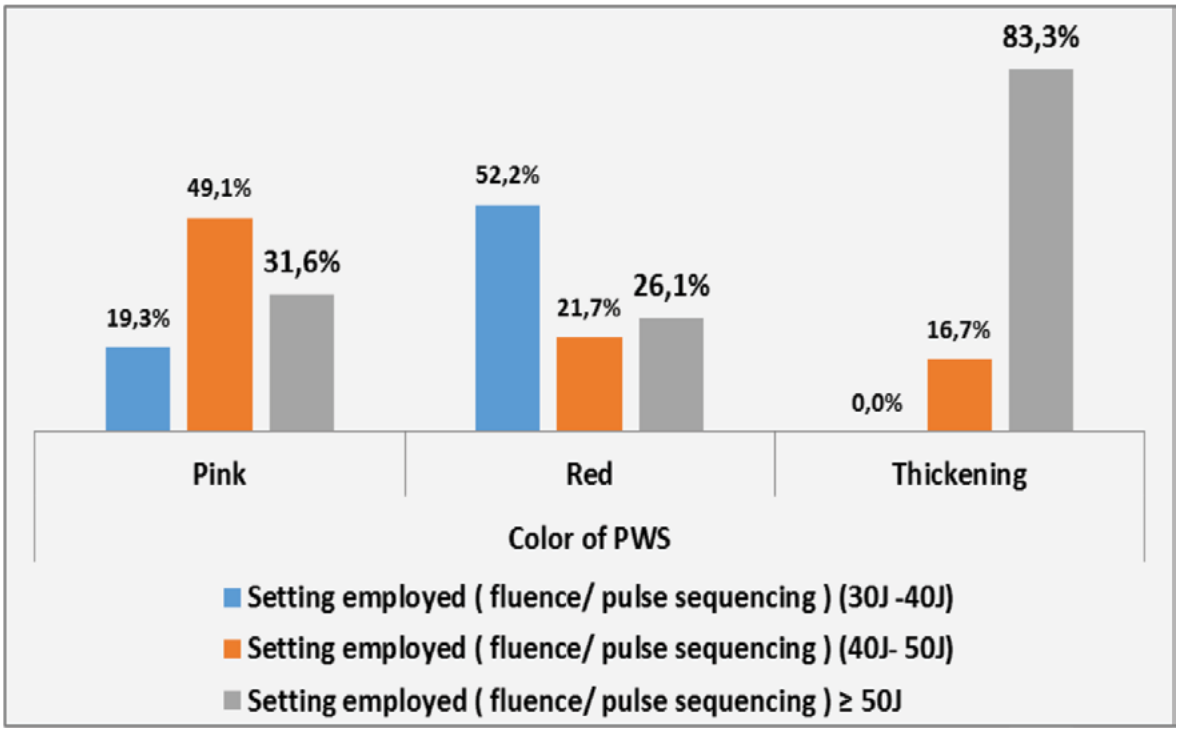


Table 25. Applied energy to different type of lesions according to their color.

The IPL has a wavelength range of 400-1400nm and can penetrate to the deeper vascular network found within a PWS. The diameter and depth of the vessels in different types of PWS are different. IPL can produce a series of different wavelengths that can treat different depth vessels, thus optimizing treatment efficacy.

In our study we tried to find where there is an association between the color of the lesion and the clearance rate. Statistical significance (Fisher's Exact Test, $p<0.001$) was found among the types and is demonstrated in Table 26.

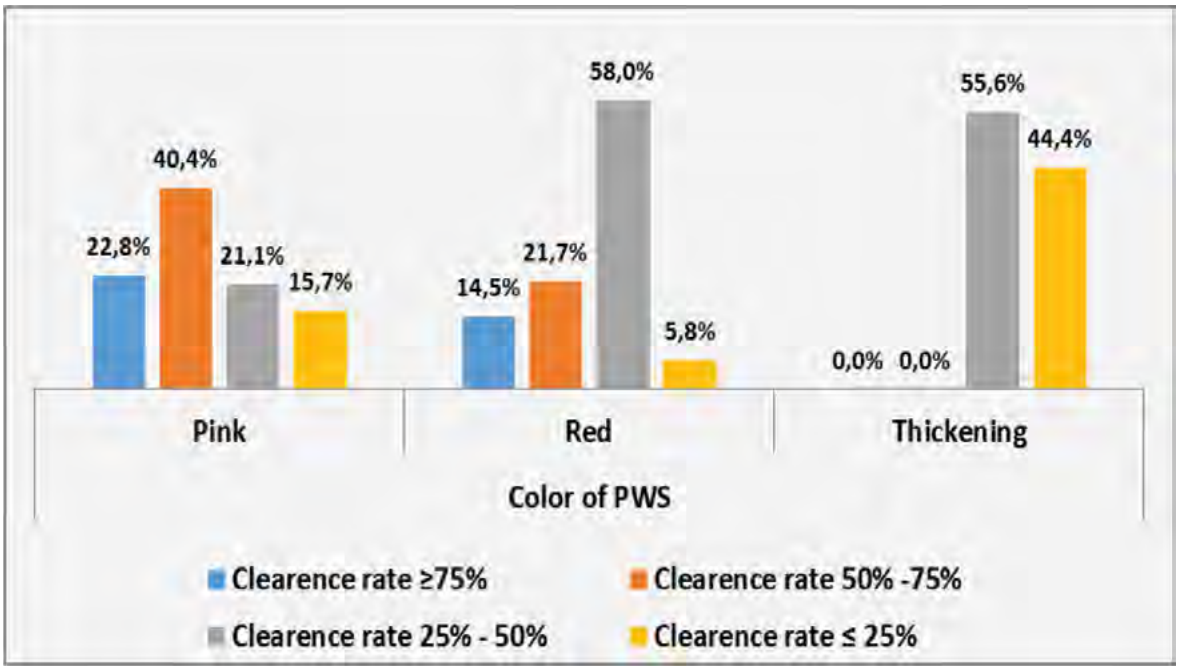


Table 26. Distribution of patients according to the color of lesions and their clearance rate.

A clearance rate more than 75% is highest in the group of patients with pink lesions- 22.8% (13/57), (Figure 24), followed by the patients with red lesions-14.5% (10/69), (Figures 25 and 26). There were no patients with this clearance rate in the last group with thickening lesions. More than 50% reduction of the lesion was achieved in the patients group with pink lesions- 40.4% (23/57) and red- 21.7% (15/69) lesions. These patients had been accepted as good responders to IPL treatments. In the group of thickening lesion there were no PWS who responded well (more than 50% clearing) to the treatments. In this group 44.4% (8/18) of lesions achieved suboptimal result with clearing rate less than 25%, (Figures 27 and 28).

Figure 24. A 17-year-old woman with a pink PWS. (A) Before treatment. (B) More than 75% clearance after four IPL treatment sessions.

Figure 25. A 28-year-old man with a red PWS. (A) Before treatment. (B) More than 50% clearance after five IPL treatment sessions.

Figure 26. A 31-year-old man with a red PWS. (A) Before treatment. (B) clearance rate is between 50%-75% after six IPL treatment sessions.

Figure 27. A 42-year-old woman with a purple thickening PWS. (A) Before treatment. (B) Less than 50% clearance after eight IPL treatment session.

Figure 28. A 51-year-old woman with a purple thickening PWS. (A) Before treatment. (B) Clearance rate between 50%-75% after seven IPL treatment sessions.

Raulin et al (123) reported good or excellent clearing on pink PWS and less impressive results on darker PWS treated with a noncoherent pulsed light source. In this study, a total of 37 patients with PWS were evaluated; seven patients had 100% clearing and 14 patients had good clearing of 70% up to 99%. Although the majority of the lesions in their study were located on the face and neck regions, the study was retrospective, and data were not collected from a single unit. In addition, identical systems and settings have not been used, and some patients had dye laser–resistant PWS.

Ozdemir et al (124) treated 11 patients with fresh facial PWS with IPL. Lesions in Patient 9 were located only on the neck region, without facial involvement. Color of lesions was pink to reddish purple. They had an overall clearing rate of 59.2% in the patients, and 47% of the patients showed moderate clinical clearing (more than 50%, less than 75%). If patients 1 and 10 who did not complete treatment are excluded, the overall response rate was 65.1%. The patients with reddish purple, red, and pink PWS had an overall clearing rate of 59.1%, 65.8%, and 82.5%, respectively. Only two patients had pink PWS in this study. Their lesions were located on the neck and right face. Complete and 65% clearing was achieved on the neck and face lesion, respectively. Their results on pink PWS contribute our results and those of Raulin et al., and the overall clearing rate is similar to the results of other IPL sources.

In 2005 Reynolds et al (125) presented the results of a 3-year prospective within patient controlled clinical trial using an intense pulsed light system called the Lumina, developed by Lynton Lasers of Cheshire, in England. Their aims and objectives were to assess the effectiveness of the system in the treatment of port wine stains in a human model and to record the optimum treatment parameters and the incidence of side effects. Following ethical approval 12 subjects were enrolled into the trial. In order to meet the requirements of the local ethics committee these were adults with port wine stains located in less visible areas of the body. The results showed that 8 of the 12 subjects had some degree of fading of their port wine stain as measured on a percentage scoring system. Of the four who failed to show any response, all had pink port wine stains. It did seem the case that the darker the port wine stain, the better the fading seen. Furthermore, the more distal lesions tended to be less responsive than those situated closer to the head area.

Fiskerstrand EJ (122) examined whether therapeutic outcome of laser treatment of PWSs has relation with their morphological parameters . Thirty patients were treated with a flashlamp-pumped pulsed dye laser. Punch biopsies were taken prior to treatment, and the biopsies were examined morphometrically. The degree of blanching was examined 6-8 weeks after treatment, and each site was retreated four times. Six patients (20%) achieved poor blanching, eight patients (27%) obtained moderate lightening and 16 patients (53%) showed good response. The vessels of the good responders were located significantly more superficially than the vessels of the moderate and poor responders. The poor responders had significantly smaller vessels than the moderate and good responders. The moderate responders had deeper, but larger vessels, than the poor responders. Hence, an increasing vessel diameter reduces the negative outcome of increasing vessel depth. The vessel diameter was correlated to the colour, e.g. the mean vessel diameter was increasing from 16.5 microns in pink lesions to 51.2 microns in purple lesions. The vessel depth was partly reflected in the lesional colour, as the pink and purple lesions had significantly deeper vessels than the red ones. These results indicate that pink lesions predict poor blanching due to deeply located small vessels, while red lesions predict a good therapeutic result because of more superficially located vessels.

The results of this study are contrary to our results and there may be a number of reasons why this is the case. One of the reason can be that it is difficult to draw any definitive statistical conclusions due to the small number of patients in the trial. Another reason could be the use of different light device in the study, e.g. PDL.

4.1.4. Location of the lesions and treatment efficacy

In our study we evaluated the relationship between the PWS location (head, neck and extremities) and the treatment efficacy. Fisher's Exact Test was applied and showed a significant statistical association ($p<0.001$) between two of the indicators (Table 27).

Clearence rate		Location of PWS			Total	p-value
		Head	Neck	Trunk/ Extremities		
≥75%	N	23	0	0	23	<0,001
	%	24,2%	0,0%	0,0%	16,0%	
50% -75%	N	24	13	1	38	
	%	25,3%	46,4%	4,8%	26,4%	
25%- 50%	N	35	15	12	62	
	%	36,8%	53,6%	57,1%	43,1%	
≤ 25%	N	13	0	8	21	
	%	13,7%	0,0%	38,1%	14,5%	
Total	N	95	28	21	144	
	%	100,0%	100,0%	100,0%	100,0%	

Table 27. Association between location of the PWS and the clearance rate.

This table shows that 24.2% (23/95) of head lesions had the greatest mean improvement (more than 75% clearing rate) contrary to the neck and extremities lesions where there were no patients with that high percentage of improvement. In the group of PWSs with neck location 46.4% (13/28) had a clearance rate between 50% to 75% and 53.6% (15/28) had a clearance rate from 25% to 50%. There were no neck lesions with more than 75% clearance so as no lesions with clearance less than 25%. Approximately 57.1% (12/21) of the extremities lesions had about 25% to 50% clearance and 38.1% (8/21) had less than 25% clearance. In this group there were only 4.8% (1/21) PWS with a clearance rate between 50%-75% which was the highest rate achieved. Regarding all these facts we may confirm that lesions on the head had better response compared to the other two groups (Figures 29-32).

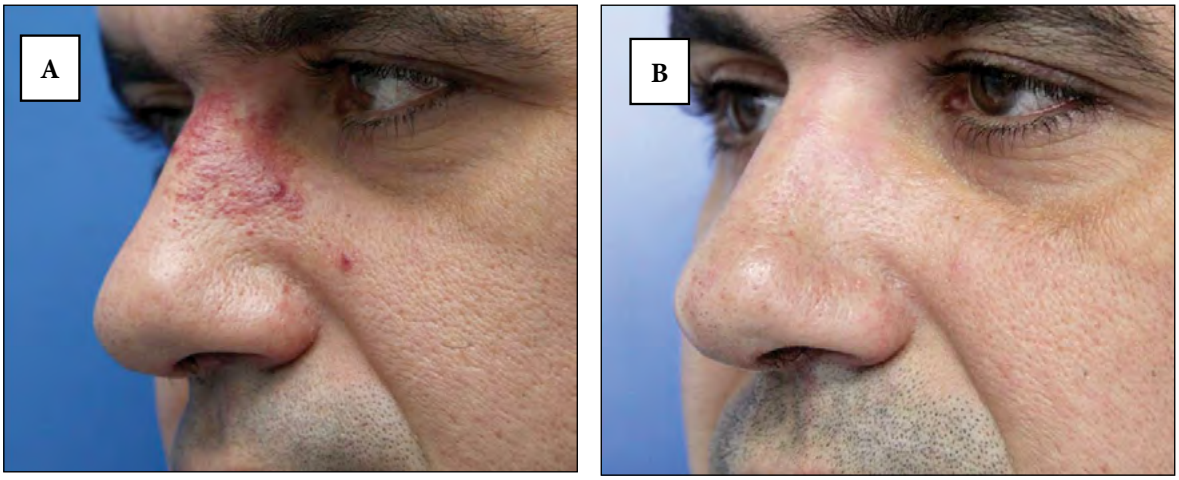


Figure 29. A 39-year old patient with head location of the PWS before (A) and after (B) two IPL treatments.

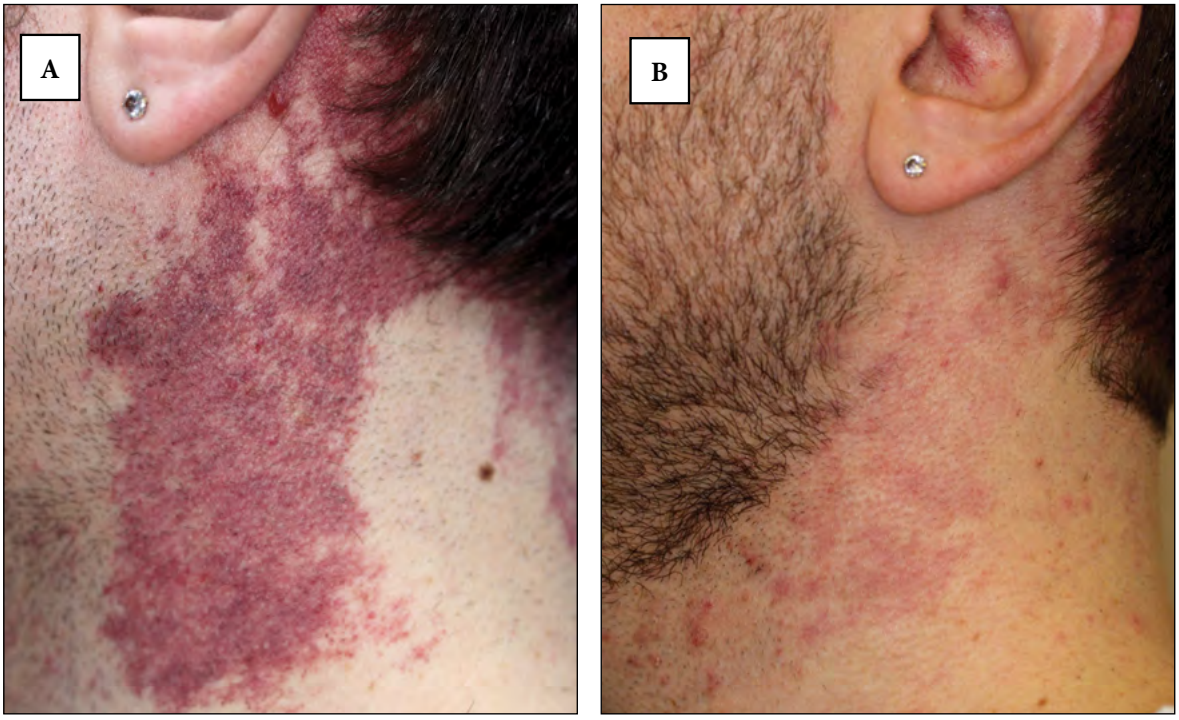


Figure 30. A 34-year old patient with neck location of the PWS before (A) and after (B) five IPL treatments.

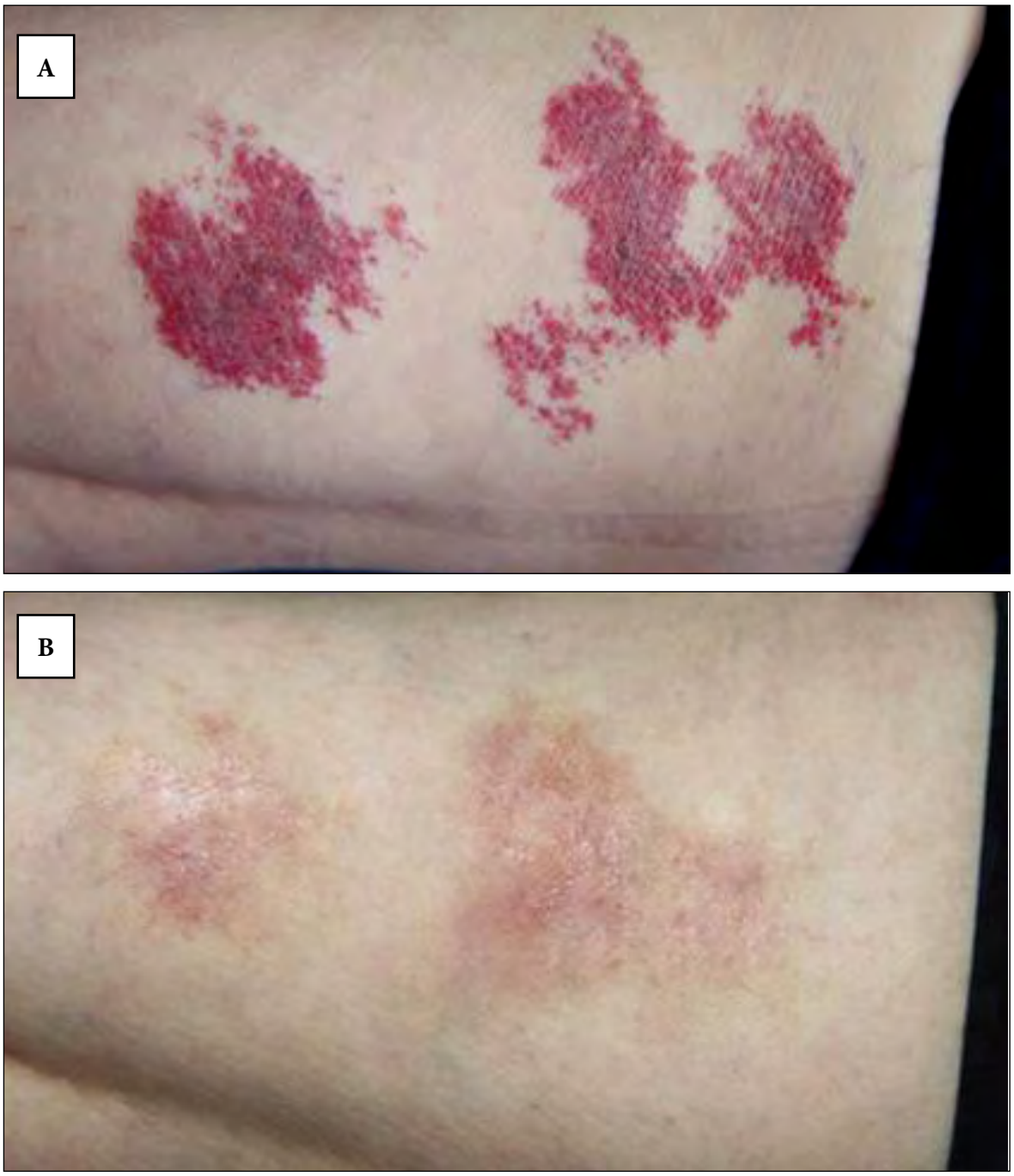


Figure 31. A 51-year old patient with leg location of the PWS before (A) and after (B) six IPL treatments, 12 months after the last procedure.

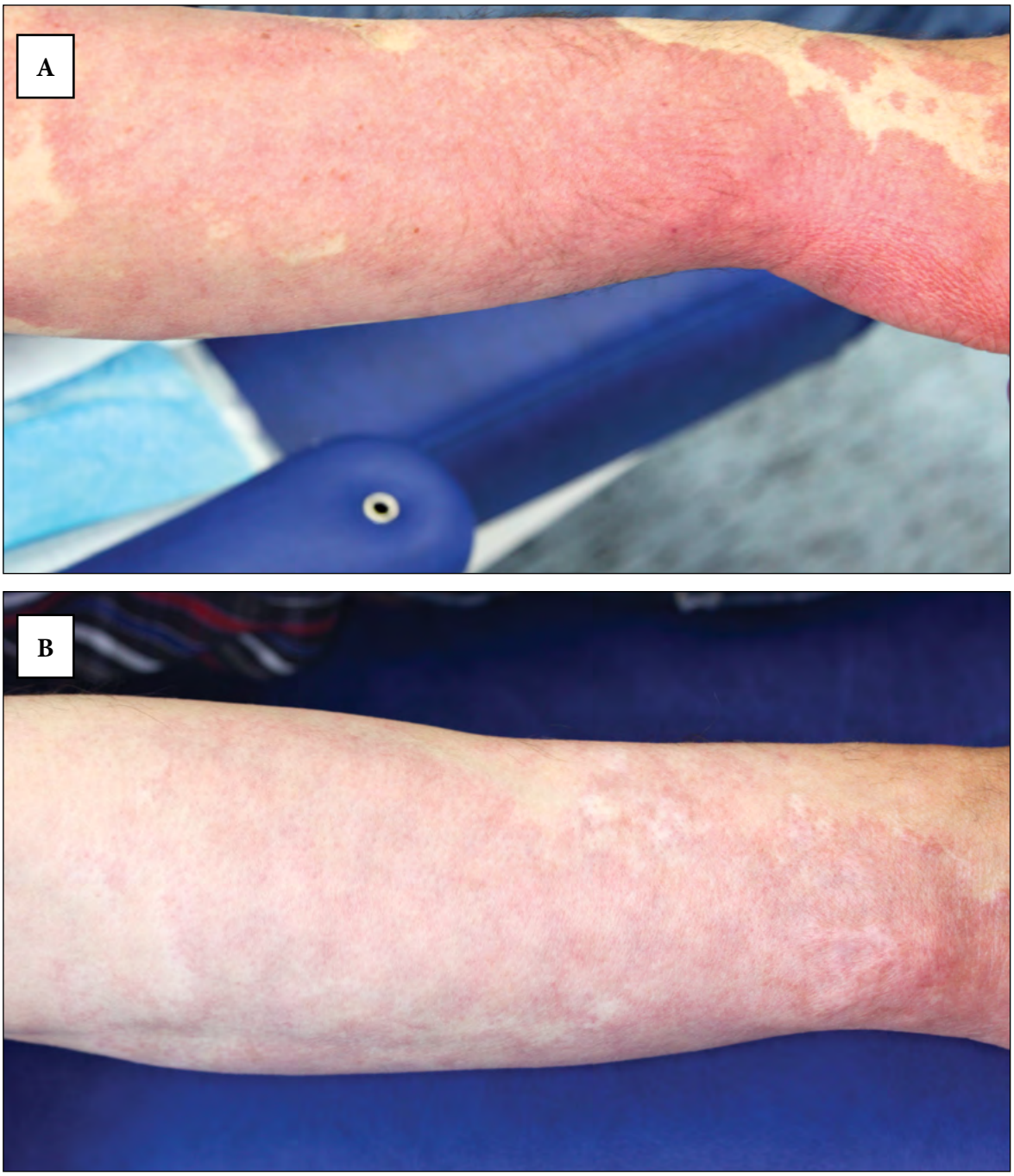


Figure 32. A 38-year old patient with arm location of the PWS before (A) and after (B) eight IPL treatments,12 months after the last procedure.

After we found out that lesions with head location seamed to present the best response to IPL treatments, we decided to examine whether different parts of the head had a different clearance rate. Through we separated the head in four categories: (i) forehead, (ii) peripheral face, (iii) central face and (iiii) mixed (Figure 19). “Forehead” comprises exclusively the central area of the forehead. “Peripheral face” comprises the lateral parts of the forehead and cheeks, temples, jaws, and the chin. “Central face” comprises the central parts of the face including the nose, upper lip and the fatty cheeks. “Mixed” PWS are combinations of central face and peripheral face lesions. The association between head location of PWS and clearance rate is depicted on Table 28.

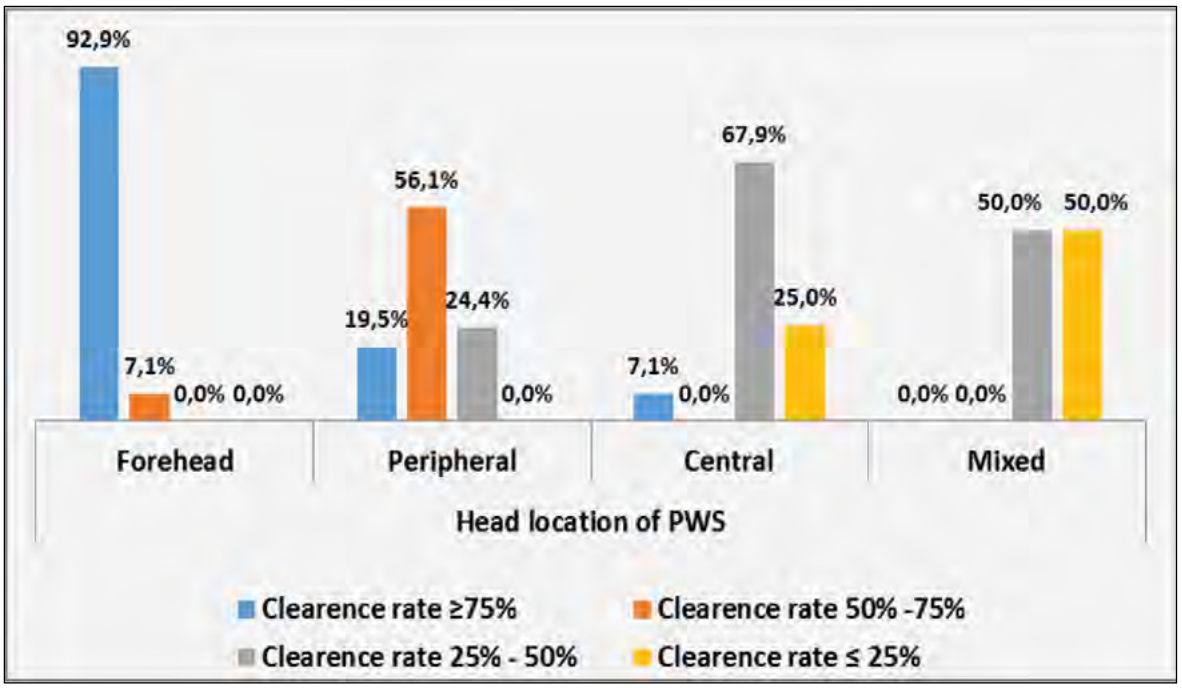


Table 28. Association between head location of PWS and clearance rate.

Our results showed that lesions on the forehead presented the best response to IPL treatments. In this group 92.9% (13/14) of PWSs had the highest clearance rate (more than 75%). Peripheral face lesions had good response: 56.1% (23/41) of them were with clearing between 50%-75% and there were none lesions with less than 25% clearance rate. In the group of central PWSs clearance was less than the previous two

groups: 67.9% (19/28) of lesions had clearance rate in range of 25%-50% and 25% (7/28) of them had a clearance rate less than 25%. A possible explanation of our results is that lesions located in the central area of the face may have abnormal vessels which were located deeper in the skin than the other anatomical areas.

Mixed lesions tended to be very large in size and showed the poorest response. In this category there were no patients with a clearance rate more than 50% (Figures 33 and 34).

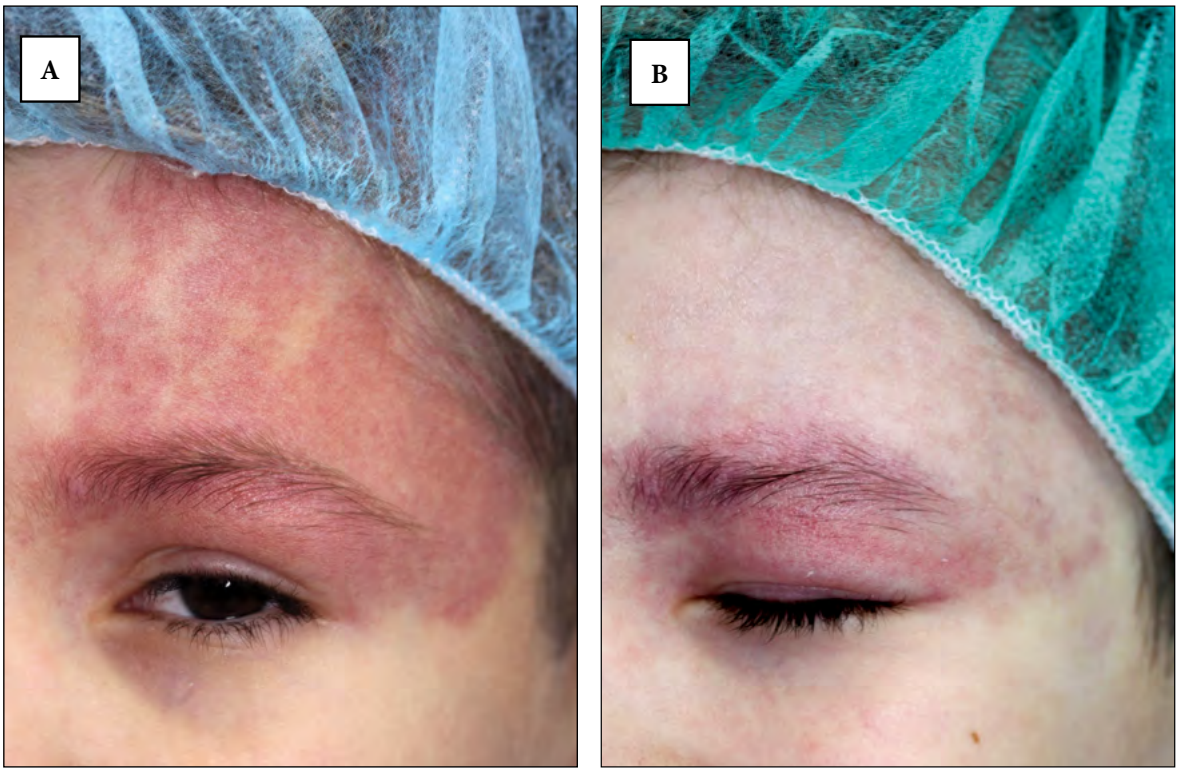


Figure 33. A 6-year old patient with PWS on the forehead before (A) and after (B) three IPL treatments- clearance rate more than 75%.

Figure 34. A 14-year old patient with PWS on central area before (A) and after (B) five IPL treatments- clearance rate more than 25%-50%.

During our research we realized that location of the PWS influenced somehow the energy that we used and the number of treatments. We applied Chi-Square Test to evalu-

ate it and found that there was a statistical significant association between the location of the lesion and the employed setting and the number of treatment (Tables 29 and 30).

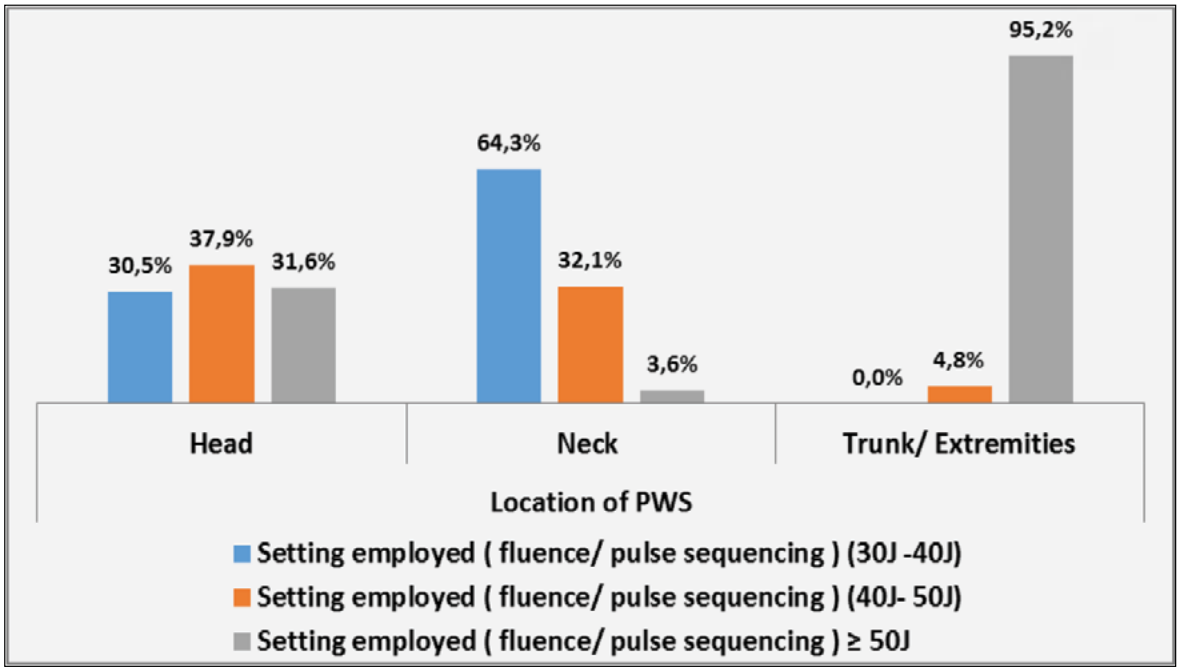


Table 29. Association between location of the lesion and the employed energy.

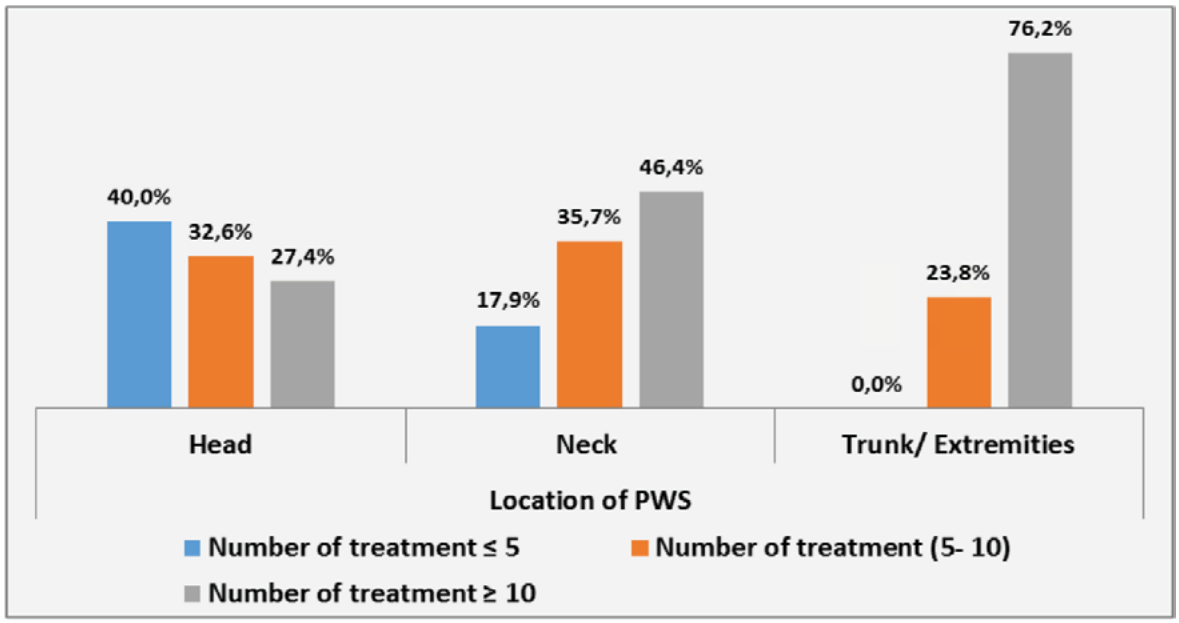


Table 30. Association between location of the lesion and the number of treatments.

In these tables it is decisively seen that lesion located on the extremities needed higher energy (more than 50J) and higher number of treatments (more than 10). In the group of neck lesions almost 64.3% (18/28) needed the lowest energy between 30J to 40J. PWSs

with head location needed the less number of procedures: 40% (38/95) of them needed 5 or less procedures. These results are important for the practitioner in order to choose the right parameters to achieve the best response of IPL treatment and to decrease the possible side effects.

All these results confirmed the findings of previous investigations about the relationship between the location of PWS and the efficacy of the response (67, 125).

In a study by Ashinoff and Geronemus (111) 12 children, aged 6 to 30 weeks, who had PWSs located on the head and neck were treated. The goal was to determine whether the earliest possible PDL treatment is more effective. Overall, the mean number of PDL treatments was 2.8±1.4.The mean percent lightening was 70.2±2.6.In all, 5 of 12 (42%) patients displayed more than 75% lightening with a mean of 3.8±1.6 treatments, 5 of 12 (42%) patients displayed 50% to 74% lightening after a mean of 2.0±0.7 treatments, and two of 12 (16%) patients displayed 26% to 49% lightening after s mean of 2.5±0.7 treatments. No patients had less than 25% lightening. In general, 10 of the 12 patients showed 50% or more lightening after a mean of 2.8±1.4 treatments. No patients exhibited scarring, atrophy, hyperpigmentation, or hypopigmentation. PWSs on the cheek or upper lip needed more treatments than those on the neck or periocular regions to achieve equivalent lightening.

A 1993 retrospective study by Renfro and Geronemus (56) analyzed whether PWSs located on different anatomic regions of the head and neck had different responses to PDL treatment. Researchers evaluated photographs of 259 adults and children before and after treatment by anatomic subdivision of the head and neck, dermatomal distribution, and midline lesions response (Figure 35).

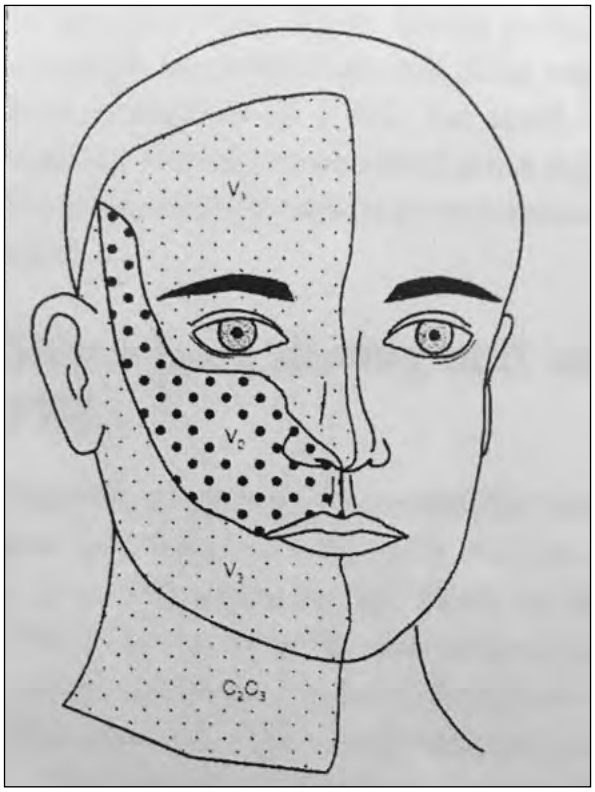


Figure 35. Dermatomal distribution of therapeutic response of PWS on adults and children after PDL treatment (126)**.**

Lightening was assessed on a scale: poor- 0% to 25% lightening, fair- 26% to 50% lightening, good- 51% to 75% lightening, and excellent indicated 76% to 100% lightening.

Renfro and Geronemus (56) described that mean lightening in the centrofacial regions had a good response (70.7%) to the PDL, whereas the remaining grouped regions had an excellent response (82.3%) to the laser. The V2 dermatomal region revealed a good response to treatment (73.8%), but this region lightened significantly less than the V1, V3 and C2/C3 regions, which had an excellent response (82.4%) when combined. Midline lesions also had an excellent response to treatment (92.4%). It is important to note that differences in anatomic regions, dermatomal distributions, and midline lesion responses were similar between adults and children, so these data were pooled.

Researchers concluded that PWSs do indeed show a differential response to PDL treatment based on anatomic location, and noted that the initial lesion color may also influence treatment response (56, 127).

Katugampola et al (128) in their five years' experience treated 640 port wine stains (PWS) with a flashlamp-pumped pulsed dye laser. One hundred and fifty-six patients have been discharged for varying reasons, of which 59 (38%) achieved excellent (at least 75%) lightening of their birthmark. Of the remaining patients, those who attended the clinic for the sixth and 12th time for treatment were also assessed to determine the degree of fading achieved in the port wine stain. Their findings confirm that flashlamp-pumped dye laser treatment is safe and effective for the treatment of PWS and that complications are rare. However, the degree of fading achieved is variable and often unpredictable. 52% of facial lesions of different colors achieved over 75% fading as against 18% of non-facial lesions. 64% of those over the age of 50 years had an excellent response whereas only 19% of those below the age of 5 years were able to achieve a similar result. The color of the port wine stain was found to be of no prognostic value. Researchers concluded also that facial lesions are responding better than non-facial lesions e.g. the lower limb, which entirely corresponds to our findings.

In 2001 Eubanks et al (129) conducted a follow-up study to determine whether anatomic location of PWSs corresponds to the depth of the ectatic vessels and affect the response to treatment. Seventeen patients presenting for evaluation or treatment of PWSs underwent videomicroscopy with a Video Loupe 7EX microscope. Data were recorded by location of the PWS as a type 1 lesion (blobs or globular structures) corresponding to ectasia of the superficial capillary loops, a type 2 lesion (rings) corresponding to ectasia of the deeper horizontal plexus, or a mixed pattern.

They found that PWSs in areas that typically respond well to laser treatment (V3, neck, and trunk) were more likely to have a superficial type 1 pattern. PWSs in areas that have a poorer response to therapy (V2, distal extremities) were more likely to have a deeper type 2 pattern. Finally they concluded that patients with lesions in the V3

dermatome and on the trunk and neck have more superficially ectatic vessels, whereas those lesions in dermatome V2 and on the distal extremities have more deeply placed vessels which explain the difference of clearing rate of PWS with different location.

Another study investigated the microscopic attributes of port-wine stains that were treated successfully with laser therapy and showed that those with a good response to treatment had significantly decreased blood vessels density and mean blood vessel diameter (130). This study was limited by small sample size. However, this finding may explain why centrofacial and limb lesions are generally less responsive to laser therapy than other regions of the face, neck, and trunk.

The results of the studies of Eubanks and Selim (38, 40) can explain our findings why head lesions respond better to IPL treatment, need fewer number of treatments and less energy than extremities lesions than lesions located on the neck and trunk regions.

4.2. Recurrence of PWS

The patients in our study were treated between November 2008 and July 2015 at the Department of Dermatology of Military Medical Academy (Sofia, Bulgaria). Efficacy of the treatments was evaluated 6 months and 12 months after the last procedure.

Having in mind that some PWSs can recur years after treatment, despite a promising response to initial treatments every patient who finished his procedures was asked to come on a follow up visit once every year. During the follow up visits of our patients we noted that some of PWSs had become darker compared to the results at the end of their treatment sessions. However, most recurrences are far less visible than the original lesion and tend to develop gradually during several years (Table 31).

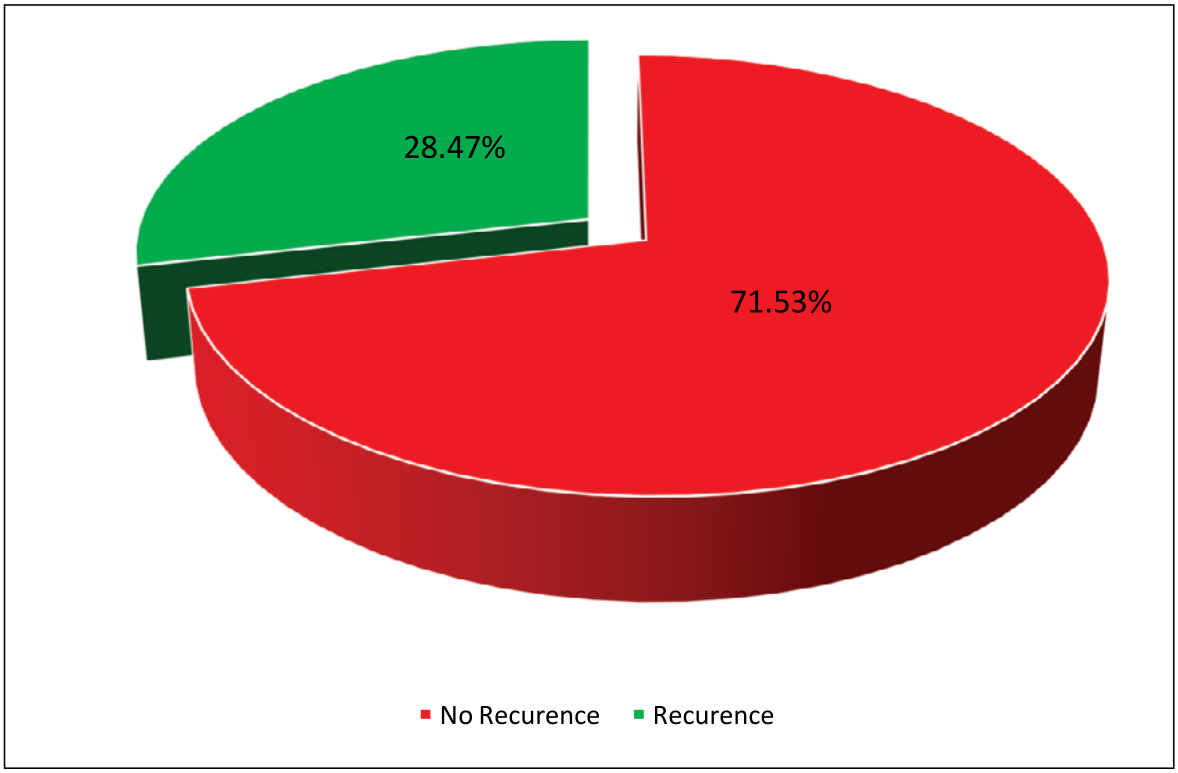


Table 31. Recurrence rate of the treated patients at 12 months.

We established that 28.47% (41/144) of all patients had recurrence, one year to three years after the end of their initial treatments. Seven (17.1%) patient's lesions had become redder 1 to 2 years after the IPL treatments. Thirteen (31.7%) patients had recurrence between 2 and 3 years after the treatments and 21 (51.2%) patients after more than 3 years. We noted that it was only focally and a new IPL treatment helped to obtain a better result. Patients reported that the redness varied according to different circumstances. One patient related the recurrence of his PWS with trauma and another referred that his lesion was not totally cleared of all red vessels after the initial treatments (Figures 36 and Figures 37).

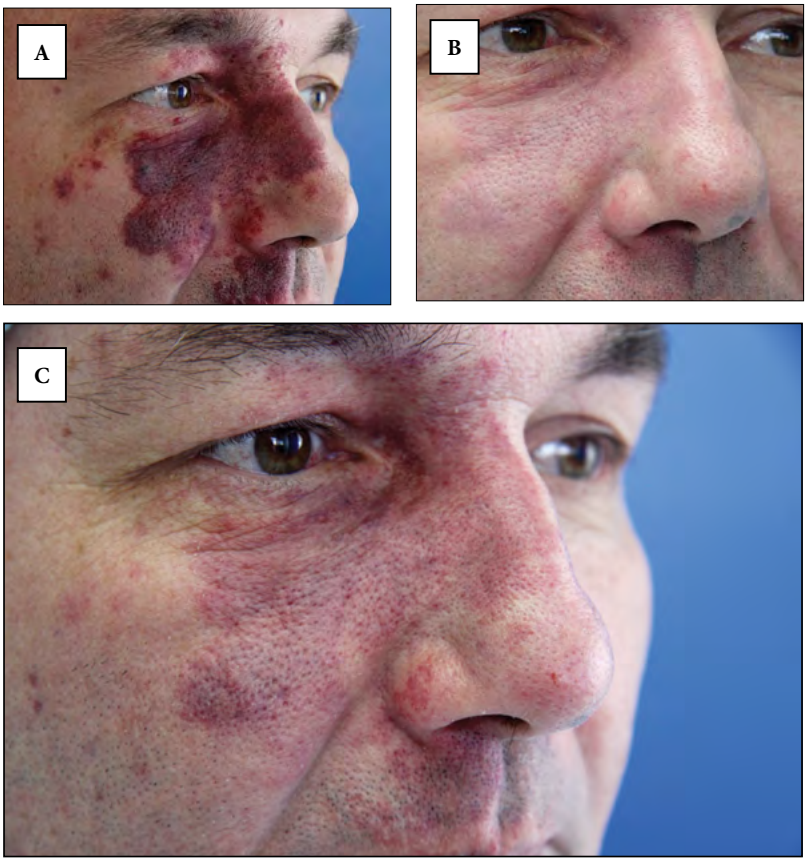


Figure 36. A 47-year old patient with PWS on central area. (A) Before treatment. (B) 12 months after the last, fifth IPL procedure. (C) Some recurrence of PWS 2 years after the last IPL procedure.

Figure 37. A 23-year old patient. (A) Before treatment. (B) 12 months after the last, seventh IPL procedure. (C) Some recurrence of PWS 2 years after the last IPL procedure.

In our survey we found that only 1 of 12 patients (8.33%) under 1 year had recurrence after the end of his treatment. In the group of children between 1 to 6 years only 5 of 41 (12.20%) had their lesions darker. Six of twenty two (27.27%) children from the age of 6 to 18 had recurrence. Contrary to the children's groups, the recurrence rate in the group of adults (older than 18 years) is much higher:29 of 69 patients (42.03%) (Table 32).

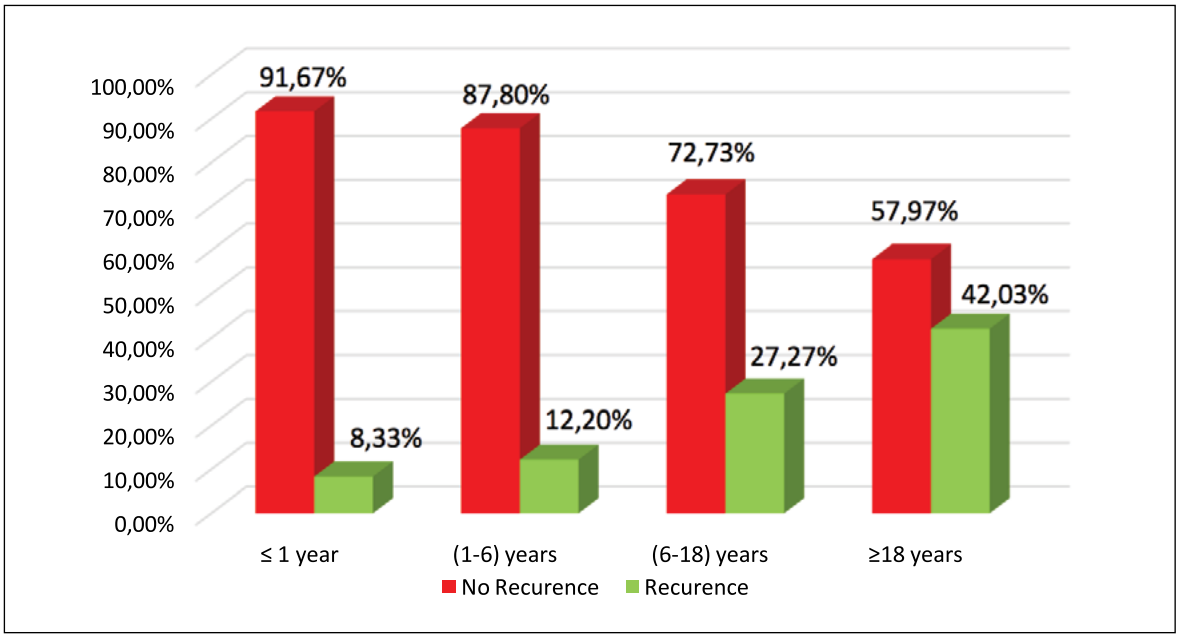


Table 32. Recurrence rate in different age groups at 12 months follow up.

We used Chi-Square Test to see whether there was statistical significant (p<0,001) association between the color of the PWSs and their recurrence (Table 33).

Recurence		Color of PWS			Total	p-value
		Pink	Red	Thickening		
Recurence	N	4	21	16	41	<0,001
	%	7,0%	30,4%	88,9%	28,5%	
No Recurence	N	53	48	2	103	
	%	93,0%	69,6%	11,1%	71,5%	
Total	N	57	69	18	144	
	%	100,0%	100,0%	100,0%	100,0%	

Table 33. Association between color and recurrence of PWS.

It is observed that only 7% (4/57) of pink lesions had recurrence, compared to 30.4% (21/69) of red and 88.9% (16/18) of thickening purple lesions. At the end, we determined that as the color of the lesions get darker the percentage of recurrence get higher.

The analysis of our results also referred that there is statistically significant association between the clearance rate of the PWS and their recurrence. Patients who have clearance rate more than 75% did not have recurrence during the follow-up period. As the clearance rate went down we had more patients whose lesions got darker. We supposed that this recurrence may be caused by the natural progressive ectasia that continues in the persistent vessels that were not destroyed during the IPL treatments. It could be also explained by the fact that the mean maximum depth of the PWS vessels is 1.00mm with a range of 0.2-3.7 mm and the limited penetration depth of the IPL.

The majority of PWS in our study did not recur following IPL treatment. The lesions with the highest risk for darkening following treatment were those with larger and deeper vessels. It is likely that this subset of patients may benefit from treatment using longer, deeper-penetrating wavelengths, such as alexandrite and Nd:YAG lasers because some vessels persist deep down in dermis and that some vessels are either too thin or too thick to be destroyed by currently available treatment methods (131,132). Individuals who do experience some darkening of their lesions following treatment will usually only require one or two treatments to clear the new vessels.

Recurrence of PWS after successful laser treatment was reported by several investigators. In 1986 Dixon et al (133) reported recurrence in 3 of 37 patients after 1-2 argon and Nd:YAG laser treatments. Thirty six of these 37 patients had residual color left in their PWS.

Orten et al (82) reported that 2 of 64 patients showed darkening of their PWS 1 year after completing therapy. At 1-2 years, 5 of 24 patients (20.8%) and 2-3 years, 4 of

10 patients (40%) showed lesional darkening. Two of 4 patients developed recurrence three years after completing laser treatment.

In 1998 Mork et al (134) observed a PWS recurrence rate of 11%. Darker PWS with larger, deeper vessels recurred more frequently, and lesions that achieved nearly complete recurred less frequently. These observations suggest that early treatment, when lesional vessels are smaller and fewer, enable greater elimination of ectatic PWS vessels when a 585 nm, 0, 45 ms pulsed dye laser is used. This laser has limited efficacy on vessels more than 1.0 mm in depth or larger than 150 μm in diameter.

In a retrospective study of 147 patients who completed lase therapy, Michel et al (92) found a 16.3% incidence of PWS recurrence, with no occurrence of lesional darkening in children who completed therapy under ten years of age. These results confirm our results that there is association between recurrence and the age of patients and also suggest that early treatment may reduce the risk of PWS recurrence.

In 2002 Ho et al (135) investigated the effect of laser treatment in chinese patients and surprisingly found no recurrence after a mean follow-up of 3.4 years, while Hansen et al (136) in their study reported that 19% of their patients had recurrence of color at 7 years of follow-up.

Using objective color measurements, Huikeshoven et al (137) performed a 10-year follow-up of a previously conducted prospective clinical study of the treatment of port-wine stains with a pulsed-dye laser. They invited the patients to undergo repeated color measurements performed by the same procedures as in the previous study. The results at long-term follow-up were compared with color measurements obtained before treatment and after completion of an average of five laser treatments of the complete port-wine stain. A questionnaire was used to investigate patient's satisfaction with the treatment and their perception of long-term changes in the stain. Of the 89 patients from whom color measurements were obtained in the previous study, 51 were included in this study.

The patients had received a median of seven additional treatment sessions since the last color measurement, which had been made after an average of five treatments. The median length of follow-up was 9.5 years. On average, the stain when measured at follow-up was significantly darker than it was when measured after the last of the initial five laser treatments (P=0.001), but it was still significantly lighter than it was when measured before treatment (P<0.001). Fifty-nine percent of patients were satisfied with the overall treatment result. Six percent of patients reported that the stain had become lighter since their last treatment, 59% that it was unchanged, and 35% that it had become darker. Huikeshoven et al (137) observed significant redarkening of port-wine stains at long-term follow-up after pulsed-dye–laser therapy, which remained the gold standard for the treatment of PWSs, and also suggest clinicians to inform patients about the possibility of redarkening before the beginning of the treatment.

In addition, a 2001 case study by Ozluer and Barlow (138) documented a 49-year-old patient who had almost total clearing with PDL treatment only to experience a partial recurrence 2.5 years later. Evidence of such recurrences suggest that PDL treatment addresses the vascular aspects of PWSs but not the underlying neurologic cause. Physicians may do well to inform patients that, in some cases laser treatment of PWSs can help manage the lesions but cannot stop their overall progression (82).

Finally considering ours and others investigators results, it is very important a good pre-counselling information to be given to the patients about the opportunity of recurrence before starting the treatment with light devices, so that they will have realistic expectations. All this means that the patient will need a “maintenance” treatment every few years in order to keep or improve the desired effect. However, we believe that the benefits of IPL therapy far outweigh the risks of no treatment. If left untreated, many port wine stains often become incompatible with normal life due to the development of bumps (vascular nodules) on the skin surface which can often bleed spontaneously with incidental trauma. Improvements in technology over the past decade, including the use

of multiple laser devices through an extended treatment protocol and selective epidermal cooling permitting the use of higher light dosages, have expedited lesion clearing. Finally, a more aggressive approach to treating infants and young children at earlier ages has also demonstrated great promise.

4.3. Final disclosure about Port Wine Stain

PWS are benign vascular lesions that mainly occur on the face or neck. Even if malignant transformation is very rare (139), the enormous cosmetic and psychological implications of PWS make treatment in the early childhood indispensable for most patients. Because of the progressive ectasia of the abnormal capillaries, with aging PWS skin usually thickens and develops nodularity and pyogenic granulomas. Most PWSs on the head and neck darken and thicken with age when exposed to UV-light (Figures 38 and Figures 39).

We evaluated that with aging in patients with PWS on the face, the upper jaw may enlarge in all 3 planes, creating an asymmetric maxilla by overgrowth and an open bite deformity in adolescents. The gum and lips may also grow larger, and this can lead to macrocheilia with lip incompetence (Figure 40), and epulis with gingival bleeding. Histologically, there is an increase in dilated capillaries and ectasias that occupy a deeper part of the reticular dermis. PWSs on the trunk or limbs generally do not undergo hypertrophic skin changes.

Progressive darkening and hypertrophy make camouflaging with makeup increasingly difficult. Furthermore, nodular lesions are more prone to spontaneous or trauma-induced bleeding and consecutive infection. The development of eruptive angiomas is a frequent complication of PWS, particularly in matured PWS, after laser treatment, and in pregnancy (152, 153). Sidwell et al. (141) postulated that the increased vasculature in PWS predisposes to the development of eczema. The authors could show in 15 out of

16 children with PWS and overlying eczematous skin changes that laser treatment was associated with improved or cleared eczema.

Figure 38. A 43-years-old patient with thickening PWS with nodules.

Figure 39. A 36-years-old patient with hypertrophic purple PWS with nodules.

Figure 40. A 27-years-old patient with thick PWS and macrocheilia.

The clinical signs underline the disfiguring aspect of PWS and account for the major impact on the quality of life of the affected individuals.

Troilius et al. (91) investigated how PWS influenced patient's life. In their retrospective study they included 163 patients with PWS treated with the PDL until there was either total clearing or until there was no further improvement. When a period from a few months to 8 years had elapsed after the treatments, the patients were given a questionnaire, which had been developed in cooperation with a psychiatrist, in order to evaluate the psychosocial implications of the PWS and the consequences of treatment. 80% of the patients more than 7 years of age had not fully accepted their PWS with increasing age and 80% thought that their life would change for the better if their PWS could be eliminated. 85% thought their PWS influenced their life

in some negative way. 45% percent of the patients considered themselves to have a lower self-esteem than their own age group. The majority of the patients considered themselves negatively influenced by their PWS. Most psychosocial parameters, such as self-esteem, contact with the opposite sex, social relationships, school contacts, the need to cover their PWS with make-up or clothes, and meeting new people, improved after PDL treatment. Older patients had higher negative scores than the younger ones, indicating the advantage of early treatment. Patients who were treated earlier with other methods producing less favorable results scored unfavorably compared to previously untreated patients. Patients with PWS treated at their clinic consider their psychosocial status to be improved after treatment and concluded that early treatment seems to be favorable for these patients.

In 2003 Hansen et al. (136) in their study evaluated the long-term efficacy of pulsed-dye laser therapy from the patient's perspective. A total of 164 patients were asked to quantify changes in their PWS as well as their psychological well-being. A formal qualitative analysis was performed on their written comments as well. The mean number of years since last treatment was 7.04. The vast majority of patients noted little or no change in texture, height, or dimension of their PWS, whereas 62% noted color improvement. A majority or patients (60%) worried less about their appearance after treatment, whereas a similar number (61%) believed their ability to make friends or meet others was unaffected by treatment. Only 19% thought others looked at or treated them differently because of their PWS. Overall, 48% of patients indicated satisfaction with treatment, 24% dissatisfaction, and 28% neutral. On a 10-point scale indicating their likelihood of recommending treatment to someone similarly affected, the mean score was 7.42. Men were significantly and consistently less satisfied with treatment than women, despite rating the degree of color improvement similarly to women. Qualitative analysis of patient comments helped validate quantitative data and revealed gender differences in satisfaction, as well as correlations

with adverse events from treatment, desire for additional treatment, and a trend toward more positive comments with the passage of time. Finally, these researchers determined that the pulsed-dye laser improves the color of PWS over long periods of time in a majority of patients. Patients tended to worry less about their appearance after treatment, although most believed treatment did not substantially affect their relationship with others or others' view of them. Most patients were satisfied or neutral with regard to satisfaction with therapy and would recommend treatment to others. A minority of patients was dissatisfied with treatment, and men were more likely to be dissatisfied. Additional long-term and prospective studies will be helpful in assessing the physical and psychosocial impact of PDL for PWS.

We are convinced that the given psychosocial implication and potential medical complication of this congenital malformation, treatment of PWS should be considered a medical necessity and covered as such by health insurance.

CONCLUSIONS

5. CONCLUSIONS

1. Intense pulsed light is a highly effective approach for treatment of port wine stains presenting different anatomical locations in patients with distinct ages and skin types.

2. Port wine stains with smaller size (less than 20 cm^2) have better response to IPL treatment than larger ones, irrespectively of patient's age.

3. The clearance rate after intense pulsed light treatment of port wine stains decreases as patient's age increases.

4. The number of treatment sessions with intense pulsed light increases with the increase of the patient's age.

5. The response rate of port wine stains to intense pulsed light differs according to their anatomical location: the lesions on the head have better response compared to those in non-facial localization, being the forehead lesions the ones with best response compared to the lesions on the central and peripheral facial areas.

6. The recurrence rate of port wine stains treated with intense pulsed light gets higher as the color of the lesions gets darker and the patient's age increases. Patients with lighter lesions and younger age tend to have lower recurrence rate.

REFERENCES

REFERENCES

1. Garzon MC, Huang JT, Enjolras O, et al. Vascular malformations: Part I. J Am Acad Dermatol. 2007 Mar;56(3):353-70; quiz 371-4.
2. Mulliken JB, Virnelli-Grevelink S. Vascular anomalies. In: Freedberg I, editor. Fitzpatrick's Dermatology in general medicine. New York: McGraw Hill; 1999. pp.
3. Mulliken JB, Young AE. Vascular Birthmarks: Hemangiomas and Malformations. Philadelphia: W. B. Saunders, 1988.
4. Shef A, Yordanov YP, Lasso JM. Vascular lesions-concepts and classifications. Med Rev. 2016;52(5):56-60.
5. Virchow R.,editor. Die Krankhaften Geschwulste. Berlin: A.Hirschwald;1863.
6. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982; 69(3):412-22.
7. Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003; 48(4):477-93; quiz 494-6.
8. Garzon MC. Infantile hemangiomas. In: Bolognia JL, Jorizzo JL, Rapini RP, senior editors. Horn TD, Mascaro JM, Saurat JH, Mancini AJ, Salasche SJ, Stingl G, editors. Dermatology. London: Mosby; 2003. p. 1599-614.
9. Jimenez GP, Flores F, Berman B, et al. Treatment of striae rubra and striae alba with the 585-nm pulsed-dye laser. Dermatol Surg 2003; 29(4):362-5.
10. Stratigos AJ, Dover JS, Arndt KA. Laser therapy. In: Bolognia JL, Jorizzo JL, Rapini RP, senior editors. Horn TD, Mascaro JM, Saurat JH, Mancini AJ, Salasche SJ, Stingl G, editors. Derma- tology. London: Mosby; 2003. p. 2153-75.
11. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues).

Adv Dermatol 1997;13: 375-423.

12. Enjolras O. Vascular malformations. In: Bolognia JL, Jorizzo JL, Rapini RP, senior editors. Horn TD, Mascaro JM, Saurat JH, Mancini AJ, Salasche SJ, Stingl G, editors. Dermatology. London: Mosby; 2003. p. 1615-29.

13. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med 1999; 341(3):173-81.

14. Cantatore JL, Kriegel DA. Laser surgery: an approach to the pediatric patient. J Am Acad Dermatol 2004; 50(2):165-84; quiz 185-8.

15. Wassef M, Blei F, Adams D, et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. Pediatrics. 2015;136(1):e203-14.

16. Folkman J. Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. N Engl J Med 1995; 333(26):1757-63.

17. Folkman J. Fundamental concepts of the angiogenic process. Curr Mol Med. 2003;3(7):643-51.

18. Savas JA, Ledon JA, Franca K, et al. Pulsed dye laser-resistant port-wine stains: mechanisms of resistance and implications for treatment. Br J Dermatol 2013;168(5)941-53.

19. Enjolras O, Riche MC MJ. Facial port-wine stains and Sturge-Weber syndrome. Pediatrics 1985; 76(1):48-51.

20. Fishman SJ, Mulliken JB. Vascular anomalies. A primer for pediatricians. Pediatr Clin North Am. 1998;45(6):1455-77.

21. Berry SA, Peterson C, Mize W, et al. Klippel-Trenaunay syndrome. Am J Med Genet 1998;79(4):319-26.

22. Burns AJ, Kaplan LC Mulliken JB. Is there an association between hemangioma

and syndromes with dysmorphic features? Pediatrics 1991;88(6):1257-67.

23. Enjolras O, Mulliken JB. The current management of vascular birthmarks. Pediatr Dermatol 1993;10(4):311-3.

24. Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. Curr Probl Pediatr 1996;26(1):3-39.

25. Du LC, Delaporte E, Catteau B, et al. Phacomatosis pigmentovascularis type II. Eur J Dermatol. 1998;8(8):569-72.

26. Barsky SH, Rosen S, Geer DE, et al. The nature and evolution of port wine stains: a computer-assisted study. J Invest Dermatol 1980;74(3):154-7.

27. Selim MM, Kelly KM, Nelson JS et al. Confocal microscopy study of nerves and blood vessels in untreated and treated port wine stains: Preliminary observations. Dermatol Surg. 2004;30(6):892-7.

28. Smoller BR RS. Port-wine stains. A disease of altered neural modulation of blood vessels? Arch Dermatol 1986;122(2):177-9.

29. Eerola I, Boon LM, Watanabe S, et al. Locus for susceptibility for familial capillary malformation ('port-wine stain') maps to 5q. Eur J Hum Genet 2002;10(6):375-80.

30. Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet 2003;73(6):1240-9.

31. Hidai C, Zupancic T, Penta K, et al. Cloning and characterization of developmental endothelial locus-1: an embryonic endothelial cell protein that binds the alphavbeta3 integrin receptor. Genes Dev 1998;12(1):21-33.

32. Sharif SA, Taydas E, Mazhar A, et al. Noninvasive clinical assessment of port-wine stain birthmarks using current and future optical imaging technology: a review. Br J Dermatol 2012;167(6):1215-23.

33. Dubois J, Garel L. Imaging and therapeutic approach of hemangiomas and vascular malformations in the pediatric age group. Pediatr Radiol 1999;29(12):879-93.

34. Troilius A. Characterisation and treatment of patients with port wine stains with special reference to the emotional impact. Univ Diss from Dep Dermatology Venereol Lund Univ. 1999;

35. Braun-Falco O, Schultze U, Meinhof W, et al. Contact radiotherapy of cutaneus hemangiomas: therapeutic effects and radiation sequelae in 818 patients. Arch Dermatol Res 1975;253(3):237-47.

36. Roe DS. Radiophosphorus in the treatment of capillary naevi. Lancet 1955;269(6900):1111-3.

37. Hliniak A, Czownicki Z, Medyńska A WZ. Long-term results and complications after the irradiation of haemangiomas in children. Radiobiol Radiother (Berl) 1966;7(2):141-4.

38. Goldwyn RM. Cutaneous laser therapy: Principles and methods.Chichester, John Wiley and Sons 1983.

39. Conway H, Montroy R. Permanent camouflage of capillary hemangiomas of face by intradermal injection of insoluble pigments (tattooing). Indications for surgery. N Y State J Med. 1965;65:876-85.

40. Grabb WC, Dingman RO, Oneal RM, et al. Facial hamartomas in children: neurofibroma, lymphangioma, and hemangioma. Plast Reconstr Surg 1980;66(4):509-27.

41. Shef A, Kadurina M. Vascular anomalies:Port wine stains and infantile hemangiomas. Light and laser devices as an effective therapeutic approach in their treatment. Dermatol and venerol 2012;1:25-35.

42. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science 1983;220(4596):524-7.

43. Principles and Practices in Cutaneous Laser Surgery. Front Cover. Arielle Kauvar, George Hruza. Taylor & Francis, Sep 20, 2005 - Medical - 840 pages.

44. Yang B, Yang O, Guzman J, et al. Intraoperative, real-time monitoring of blood flow dynamics associated with laser surgery of port wine stain birthmarks. Lasers Surg Med 2015;47(6):469-75.

45. Anderson RR. Laser-tissue interactions.Cutaneous laser surgery: The art and science of selective photothermolysis. F.R. Goldman MP.St.Louis, Mosby Inc 1999: pp1-18.

46. Hruza G. Laser Physics and Tissue interaction. American Academy of Dermatology, New Orleans 1999.

47. Castro DJ. The physical principles of lasers.Cutaneous laser surgery. Apfelberg DB. New York, Raven Press1992: pp1-11.

48. Dover JS, Arndt KA, Geronemus RG, et al. Understanding lasers. Illustrated cutaneous laser surgery, a practitioner's guide.Percy RC and Davis KW.Norwalk, Connecticut,Appleton&Large 1990: pp2-19.

49. Anderson RR, Parrish JA. "The optics of the skin". J Invest Dermatol. 1981;77(1):13-9.

50. Bae YS, Ng E, Geronemus RG. Successful treatment of two pediatric port wine stains in darker skin types using 595 nm laser. Lasers Surg Med 2016;48(4):339-42.

51. Garden JM, Polla LL, Tan OT. The treatment of port-wine stains by the pulsed dye laser. Analysis of pulse duration and long-term therapy. Arch Dermatol 1988; 124(6):889–96.

52. Taieb A, Touati L, Cony M, et al. Treatment of port- wine stains with the 585-nm flashlamp-pulsed tunable dye laser: a study of 74 patients. Dermatology 1994;188(4):276–81.

53. Wlotzke U, Hohenleutner U, Abd-El-Raheem TA, et al. Side-effects and complications of flashlamp-pumped pulsed dye laser therapy of port-wine stains. A prospective study. Br J Dermatol 1996;134(3):475–80.

54. Ortiz AE, Nelson JS. Port-wine stain laser treatments and novel approaches. Facial Plast Surg 2012;28(6):611-20.

55. Zenzie HH, Altshuler GB, Smirnov MZ, et al. Evaluation of cooling methods for laser dermatology. Lasers Surg Med 2000;26(2):130–44.

56. Renfro L, Geronemus RG. Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. Arch Dermatol 1993:129(2):182–8.

57. Srinivas CR, Kumaresan M. Lasers for vascular lesions: standard guidelines of care. Indian J Dermatol Venereol Leprol 2011;77(3):349-68.

58. Adamic M, Troilius A, Adatto M, et al. Vascular lasers and IPLS: guidelines for care from the European Society for Laser Dermatology (ESLD). J Cosmet Laser Ther 2007;9 (2):113–24.

59. Tan OT, Stafford TJ. Treatment of port-wine stains at 577 nm: clinical results. Med Instr 1987; 21(4):218-21.

60. Tan OT, Morrison P, Kurban AK. 585 nm for the treatment of port wine stains. Plast Reconstr Surg 1990;86(6):1112-7.

61. Reyes BA, Geronemus R.Treatment of port wine stains during chlidhood with the flashlamp-pumped pulsed dye laser.J Am Acad Dermatol 1990; 23(6 Pt 1):1142-8.

62. Griffin TD Jr, Foshee JP, Finney R, et al. Port wine stain treated with a combination of pulsed dye laser and topical rapamycin ointment. Lasers Surg Med 2016;48(2):193-6.

63. Yu W, Ma G, Qiu Y, et al. Prospective comparison treatment of 595-nm pulsed-dye lasers for virgin port-wine stain. Br J Dermatol 201;172(3):684-91.

64. Ashinoff R,Geronemus RG.Treatment of a port wine stain in a black patient with the pulsed dye laser. J Dermatol Surg Oncol 1992;18(2):147-8.

65. Kao B, Kelly KM, Aguilar G, et al. Evaluation of cryogen spray cooling exposure on in vitro model human skin. Laser Surg Med 2004; 34(2):146-54.

66. Chen JK, Ghasri P, Aguilar G, et al. An overview of clinical and experimental treatment modalities for port wine stains. J Am Acad Dermatol 2012;67(2):289–304.

67. Bjerring P, Christiansen K, Troilius A. Intense pulsed light source for the treatment of dye laser resistant port-wine stains. J Cosmet Laser Ther 2003;5(1):7-13.

68. Chowdhury MM, Harris S, Lanigan SW. Potassium titanyl phosphate laser treatment of resistant port-wine stains. Br J Dermatol 2001;144(4):814–7.

69. Li L, Kono T, Groff WF, et al. Comparison study of a long-pulse pulsed dye laser and a long-pulse pulsed alexandrite laser in the treatment of port wine stains. J Cosmet Laser Ther. 2008; 10(1):12-5.

70. Izikson L, Nelson JS, Anderson RR. Treatment of hypertrophic and resistant port-wine stains with a 755 nm laser: a case series of 20 patients. Lasers Surg Med 2009;41(6):427–32.

71. Izikson L, Nelson JS, Anderson RR. Treatment of hypertrophic and resistant port wine stains with a 755 nm laser: a case series of 20 patients. Lasers Surg Med. 2009; 41(6):427-32.

72. Lee HR, Han TY, Kim YG, et al. Clinical experience in the treatment of port-wine stains with blebs. Ann Dermatol 2012;24(3):306-10.

73. Yang MU, Yaroslavsky AN, Farinelli WA, et al. Long-pulsed neodymium:yttrium-aluminum-garnet laser treatment for port-wine stains. J Am Acad Dermatol. 2005; 52(3 Pt 1):480-90.

74. Al-Dhalimi MA, Al-Janabi MH. Split lesion randomized comparative study be-

tween long pulsed Nd:YAG laser 532 and 1,064 nm in treatment of facial port-wine stain. Lasers Surg Med 2016;48(9):852-8.

75. Reddy KK, Brauer JA, Idriss MH, et al. Treatment of port-wine stains with a short pulse width 532-nm Nd:YAG laser. J Drugs Dermatol 2013;12(1):66-71.

76. Weiss RA, Weiss MA. Noncoherent Light Source. In: Kauvar A, Hruza G, eds. Principles and Practice in Cutaneous Laser Surgery. Taylor&Francis Group LLC, NW 2005, pp355-361.

77. Wang B, Wu Y, Zhu X, et al. Treatment of neck port-wine stain with intense pulsed light in Chinese population. J Cosmet Laser Ther 2013;15(2):85-90.

78. Klein A, Bäumler W, Landthaler M, et al. Laser and IPL treatment of port-wine stains: Therapy options, limitations, and practical aspects. Lasers Med Sci. 2011;26(6):845–59.

79. Owens WW 3rd, Lang PG. Herpes simplex infection and colonization with Pseudomonas aeruginosa complicating pulsed- dye laser treatment. Arch Dermatol 2004;140(6):760–1.

80. Chen T, Frieden IJ. Development of extensive flat warts after pulsed dye laser treatment of a port-wine stain. Dermatol Surg 2007;33(6):734–5.

81. Wimmershoff MB, Wenig M, Hohenleutner U, et al. Treatment of port-wine stains with the flash lamp pumped dye laser. 5 years of clinical experience. Hautarzt 2001;52(11):1011–5.

82. Orten SS, Waner M, Flock S, et al. Port-wine stains. An assessment of 5 years of treatment. Arch Otolaryngol Head Neck Surg 1996;122(11):1174–9.

83. Sommer S, Seukeran DC, Sheehan-Dare RA . Efficacy of pulsed dye laser treatment of port-wine stain malformations of the lower limb. Br J Dermatol 2003;149(4):770–5.

84. Hennedige AA, Quaba AA, Al-Nakib K. Sturge-Weber syndrome and dermatomal

facial port-wine stains: incidence, association with glaucoma, and pulsed tunable dye laser treatment effecti v ene s s. Plast R econstr Surg 2008;121(4):1173 -80 .

85. Thajudheen CP, Jyothy K, Priyadarshini A. Treatment of port-wine stains with flash lamp pumped pulsed dye laser on Indian skin: a six year study. J Cutan Aesthet Surg 2014;7(1);32-6.

86. Namba Y, Mae O, Ao M. The treatment of port-wine stains with a dye laser: a study of 644 patients. Scand J Plast Reconstr Surg Hand Surg 2001;35(2):197–202.

87. Nagore E, Requena C, Sevila A, et al. Thickness of healthy and affected skin of children with port-wine stains: potential repercussions on response to pulsed dye laser treatment. Dermatol Surg. 2004;30(12 Pt 1):1457-61.

88. Babilas P, Shafirstein G, Baumler W, et al. Selective photothermolysis of blood vessels following flashlamp-pumped pulsed dye laser irradiation: in vivo results and mathematical modelling are in agreement. J Invest Dermatol. 2005;125(2):343-52.

89. Prahl S. Optical absorption of hemoglobin. http://omlc.ogi. edu/spectra/hemoglobin/. 1999.

90. Black JF, Barton JK. Chemical and structural changes in blood undergoing laser photocoagulation. Photochem Photobiol 2004;80:89–97.

91. Troilius A, Wrangsjo B, Ljunggren B. Patients with port- wine stains and their psychosocial reactions after photothermolytic treatment. Dermatol Surg 2000;26(3):190–6.

92. Michel S, Landthaler M, Hohenleutner U. Recurrence of port-wine stains after treatment with the flashlamp-pumped pulsed dye laser. Br J Dermatol 2000;143(6):1230–4.

93. Huikeshoven M, Koster PH, de Borgie CA, et al. Redarkening of port-wine stains 10 years after pulsed-dye-laser treatment. N Engl J Med 2007;356(12):1235–40.

94. Hansen K, Kreiter CD, Rosenbaum M, et al. Long-term psychological impact and perceived efficacy of pulsed-dye laser therapy for patients with port-wine stains. Dermatol Surg 2003;29(1):49–55.

95. Li G, Lin T, Wu Q, et al. Clinical analysis of port wine stains treated by intense pulsed light. J Cosmet Laser Ther. 2010;12(1):2–6.

96. Verkruysse W, Majaron B, Tanenbaum BS, et al. Optimal cryogen spray cooling parameters for pulsed laser treatment of port-wine stains. Lasers Surg Med 2000;27(2):165–70.

97. Klein A, Bäumler W, Landthaler M, et al. Laser and IPL treatment of port-wine stains: therapy options, limitations, and practical aspects. Lasers Med Sci 2011;26(6):845-59.

98. Garden JM. Laser removal of port-wine stains: how close are we? A Commentary. Lasers Surg Med 2007;39(7):569–70.

99. Szychta P, Al-Nakib K, Anderson W, et al. Quantitative method for evaluation of aesthetic results after laser treatment for birthmarks. Lasers Med Sci. 2013;28(6):1567–72.

100. Goldman MP, Fitzpatrick RE, Ruiz-Esparza J. Treatment of port-wine stains (capillary malformation) with the flashlamp-pumped pulsed dye laser. J Pediatr 1993;122(1):71-7.

101. Yates F. Contingency table involving small numbers and the $\chi 2$ test. Supplement to the Journal of the Royal Statistical Society 1934;1(2): 217–35.

102. Ryabko BY, Stognienko VS, Shokin YI. A new test for randomness and its application to some cryptographic problems. J Stat Plan Inference 2004;123: 365–76.

103. Fisher RA. On the interpretation of $\chi 2$ from contingency tables, and the calculation of P. J R Stat Soc 1922;85(1):87–94.

104. Larntz K. Small-sample comparisons of exact levels for chi-squared goodness-of-fit statistics. J Am Stat Assoc. 1978;73(362):253–63.

105. Mehta CR, Patel NR, Tsiatis AA. Exact significance testing to establish treatment equivalence with ordered categorical data. Biometrics 1984;40(3):819–25.

106. Mehta CR, Patel NR. A Network Algorithm for Performing Fisher's Exact Test in r Xc Contingency Tables. J Am Stat Assoc. 1983;78(382):427–34.

107. Mehta CR, Patel NR. Algorithm 643: Fexact: a Fortran subroutine for Fisher's exact test on unordered r×c contingency tables. ACM Trans Math Softw 1986;12 (2): 154–61.

108. Nguyen CM, Yohn JJ, Huff C, et al. Facial port wine stains in childhood: prediction of the rate of improvement as a function of the age of the patient, size and location of the port wine stain and the number of treatments with the pulsed dye (585 nm) laser. Br J Dermatol 1998;138(5):821-5.

109. Yohn JJ, Huff JC, Aeling JL, et al. Lesion size is a factor for determining the rate of port-wine stain clearing following pulsed dye laser treatment in adults. Cutis 1997;59(5):267-70.

110. Morelli JG1, Weston WL, Huff JC, et al. Initial lesion size as a predictive factor in determining the response of port-wine stains in children treated with the pulsed dye laser. Arch Pediatr Adolesc Med 1995;149(10):1142-4.

111. Ashinoff R, Geronemus RG. Flashlamp-pumped pulsed dye laser for port-wine stains in infancy: earlier versus later treatment. J Am Acad Dermatol 1991;24(3):467-72.

112. Tan OT, Sherwood K, Gilchrest BA.Treatment of children with PWS using the flashlamp-pulsed tunable dye laser. New Engl J Med 1989;320(7):416-21.

113. Alster TS, Wilson F. Treatment of port-wine stains with the flashlamp-pumped pulsed dye laser: extended clinical experience in children and adults. Ann Plast Surg 1994;32(5):478-84.

114. van der Horst CM, Koster PH, de Borgie CA, et al. Effect of the Timing of Treatment of Port-Wine Stains with the Flash-Lamp–Pumped Pulsed-Dye Laser. N Engl J Med 1998; 338(15):1028-33.

115. Barsky SH, Rosen S, Geer DE, et al. The nature and evolution of port-wine stains: a computer-assisted study. J Invest Dermatol 1980;74(3):154–7.

116. Lanigan SW, Cotterill JA. Psychological disabilities amongst patients with port wine stains. Br J Dermatol 1989;121(2):209-15.

117. Zhong SX, Liu YY, Yao L, et al. Clinical analysis of port-wine stain in 130 Chinese patients treated by long-pulsed 1064-nm Nd: YAG laser. J Cosmet Laser Ther 2014;16(6):279-83.

118. Geronemus RG.Pulsed dye laser treatment of vascular lesions in children. J Dermatol Surg Oncol 1993;19(4):303-10.

119. Reyes BA, Geronemus R. Treatment of port-wine stains during childhood with the flashlamp-pumped pulsed dye laser. J Am Acad Dermatol 1990;23(6 Pt 1):1142-8.

120. Morelli JG. Pulsed dye laser treatment of port-wine stains in children. In: Management Treatment benign cutaneus Vascular Lesions; Philadelphia, Lea&Febiger,1992.

121. Fitzpatrick RE, Lowe NJ, Goldman MP, et al. Flashlamp-pumped pulsed dye laser treatment of port-wine stains. J Dermatol Surg Oncol 1994;20(11):743–8.

122. Fiskerstrand EJ, Svaasand LO, Kopstad G, et al. Laser treatment of port wine stains: therapeutic outcome in relation to morphological parameters. Br J Dermatol 1996;134(6):1039-43.

123. Raulin C, Schroeter CA, Weiss RA, et al. Treatment of port-wine stains with a noncoherent pulsed light source: a retrospective study. Arch Dermatol 1999;135(6):679-83.

124. Ozdemir M, Engin B, Mevlitoğlu I. Treatment of facial port-wine stains with intense pulsed light: a prospective study. J Cosmet Dermatol 2008;7(2):127-31.

125. Reynolds N, Exley J, Hills S, et al. The role of the Lumina intense pulsed light system in the treatment of port-wine stains–a case controlled study. Br J Plast Surg 2005;58(7):968–80.

126. Renfro L,Geronemus RG. Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. Arch Dermatol 1993;129(2):182-8.

127. Yu W, Ma G, Qiu Y, et al. Why do port-wine stains (PWS) on the lateral face respond better to pulsed dye laser (PDL) than those located on the central face? J Am Acad Dermatol 2016;74(3):527-35.

128. Katugampola GA, Lanigan SW. Five years' experience of treating port wine stains with the flashlamp-pumped pulsed dye laser. Br J Dermatol 1997;137(5):750-4.

129. Eubanks LE, McBurney EI. Videomicroscopy of port-wine stains: correlation of location and depth of lesion. J Am Acad Dermatol 2001;44(6);948-51.

130. Selim MM, Kelly KM, Nelson JS, et al. Confocal microscopy study of nerves and blood vessels in untreated and treated port wine stains: preliminary observations. Dermatol Surg 2004;30(6):892-7.

131. McBurney EI. Side effects and complications of laser therapy. Dermatol Clin. 2002;20(1):165-76.

132. Shef A, Yordanov Y, Kadurina M. Infantile hemangiomas: contemporary concepts and laser treatment. Mil Med. 2013;55(3-4):7–11.

133. Dixon JA, Gilbertson JJ. Argon and neodymium YAG laser therapy of dark nodular port wine stains in older patients. Lasers Surg Med 1986;6(1);5-11.

134. Mork NJ, Austad J. Do port wine stains recur after successful treatment with pulsed dye laser. J Eur Acad Dermatol Venereol 1998;11:S142-S143.

135. Ho WS, Chan HH, Ying SY, et al. Laser treatment of congenital facial port-wine stains: long-term efficacy and complication in Chinese patients. Lasers Surg Med 2002;30(1):44-7.

136. Hansen K, Kreiter CD, Rosenbaum M, et al. Long-term psychological impact and perceived efficacy of pulsed-dye laser therapy for patients with port-wine stains. Dermatol Surg 2003;29(1):49-55.

137. Huikeshoven M, Koster PH, de Borgie CA, et al. Redarkening of Port-Wine Stains 10 Years after Pulsed-Dye–Laser Treatment. N Engl J Med. 2007;356(12):1235-40.

138. Ozluer SM, Barlow RJ. Partial re-emergence of a port-wine stain following successful treatment with flashlamp-pumped dye laser. Clin Exp Dermatol 200;26(1):37-9.

139. Silapunt S, Goldberg LH, Thurber M, et al. Basal cell carcinoma arising in a port-wine stain. Dermatol Surg. 2004;30(9):1241–5.

140. Kavak A, Alper M, Aydogan I. Port-wine stain, laser therapy and pregnancy: risk factors for multiple pyogenic granulomas? J Eur Acad Dermatol Venereol 2007;21(7):1003–4.

141. Sidwell RU, Syed S, HarperI. Port-wine stains and eczema. Br J Dermatol 2001;144(6):1269–70.

ANNEXES

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В ПОМОЩ НА ПРАКТИКАТА
HELPING PRACTICE

Vascular lesions – concepts and classifications

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Съдови лезии – схващания и класификации

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Summary:

Vascular lesions are heterogeneous group of anomalies with different clinical behavior and histopathological features although many times they look quite similar. The adequate diagnosis is of paramount importance for the appropriate management. From the other hand, historically the descriptive and histologic terms have led to confusion in the communication among medical professionals involved in the treatment and investigation of this group of diseases. The aim of the present article is to make a brief review of the main classifications of vascular anomalies stressing on the most contemporary concepts in the taxonomy of this motley group of lesions.

Key words: vascular lesions, vascular anomalies, classification, hemangiomas, port wine stains.

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Резюме:

Съдовите лезии са хетерогенна група аномалии с различна клинична картина и хистопатологични характеристики, въпреки че често изглеждат твърде сходни. Адекватната диагноза е от първостепенно значение за правилното им третиране. От друга страна, погледнато в исторически план, натрупването на множество описателни и хистологични термини води до неяснота в комуникацията между медицинските специалисти, участващи в лечението и проучванията на тази група заболявания. Целта на настоящата статия е да се направи кратък преглед на основните класификации на съдовите аномалии, като се постави акцент върху най-съвременните концепции в таксономията на тази разнородна група лезии.

Key words: съдови лезии, съдови аномалии, класификация, хемангиоми, порт уайн стейнс

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Infantile hemangiomas: contemporary concepts and laser treatment

ДЕТСКИ ХЕМАНГИОМИ: СЪВРЕМЕННИ ВИЖДАНИЯ И ЛАЗЕРНО ТРЕТИРАНЕ

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INFANTILE HAEMANGIOMAS: CONTEMPORARY CONCEPTS AND LASER TREATMENT

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РЕЗЮМЕ

Детските хемангиоми (ДХ) са най-честите тумори в кърмаческа възраст и детството. Повечето ДХ нямат съществено клинично значение. Една част от тях обаче се нуждаят от лечение, поради взаимовръзката им с жизненоважни структури, рискът от обезобразяване, разязвяване или кървене. В настоящата статия е направен кратък преглед на съвременните концепции, дефиниции и класификации на ДХ. Засегнати са спорни въпроси, свързани с целите и показанията за лечение. Специален акцент е поставен върху най-съвременния метод за лечение на тези лезии – лазерите.

Ключови думи: СЪДОВИ АНОМАЛИИ, ДЕТСКИ ХЕМАНГИОМИ, ЛЕЧЕНИЕ, ЛАЗЕРИ

SUMMARY

Infantile haemangiomas (IH) are the most common tumors of infancy and childhood. Most IH are medically insignificant; however, a proportion will require treatment because of interference with vital structures, threat of significant disfigurement, ulceration, or bleeding. This article reviews briefly current concepts, definitions and classifications of IH. The most controversial issues regarding the purposes and indications for treatment are discussed. Special emphasis is put on the most contemporary treatment of these lesions with laser systems.

Keywords: VASCULAR ANOMALIES, INFANTILE HAEMANGIOMAS, TREATMENT, LASERS

Терминът "съдови аномалии" включва множество състояния, резултат от нарушения в съдовата морфогенеза, като съдовите аномалии на кожата много често и неправилно се описват от клиницистите с общият термин "хемангиоми" [1]. Съдовите аномалии се разделят на хемангиоми и съдови малформации въз основа на биологичното им поведение и патогенеза [2]. Според модификацията на тази класификация от 1996 г. съдовите аномалии са разделени на съдови тумори и съдови малформации /табл. 1/ [3].

Таблица 1. ▼ *Класификация на съдовите аномалии, приета от Международната асоциация за изследване на съдови аномалии (ISSVA)*

Table 1. Updated International Society for the Study of Vascular Anomalies (ISSVA) classification of vascular anomalies

Vascular tumors	Vascular malformations
Infantile hemangiomas	Slow-flow vascular malformations
Congenital hemangiomas (RICH and NICH)	Capillary malformation (CM)
Tufted angioma (with or without Kasabach–Merritt syndrome)	Port-wine stain
Kaposiform hemangioendothelioma (with or without Kasabach–Merritt syndrome)	Telangiectasia
Spindle cell hemangioendothelioma	Angiokeratoma
Other, rare hemangioendotheliomas (e.g. epithelioid, composite, retiform, polymorphous, Dabska tumor lymphangioendotheliomatosis)	Venous malformation (VM)
Dermatological acquired vascular tumors (e.g. pyogenic granuloma, targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma)	Common sporadic VM
	Bean syndrome
	Familial cutaneous and mucosal venous malformation (VMCM)
	Glomuvenous malformation (GVM) (glomangioma)
	Maffucci syndrome
	Lymphatic malformation (LM)
	Fast-flow vascular malformations
	Arterial malformation (AM)
	Arteriovenous fistula (AVF)
	Arteriovenous malformation (AVM)
	Complex-combined vascular malformations
	CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM

C, capillary; V, venous; L, lymphatic; AV, arteriovenous; M, malformation; RICH, rapidly involuting congenital hemangioma; NICH, non-involuting congenital hemangioma.

Особен интерес за клиничната практика представляват детските хемангиоми (ДХ) – най-честите доброкачествени тумори в кърмаческа и детска възраст [4]. Приблизително 80-90% от ДХ се проявяват през първите 4 седмици от живота от прекурсорна лезия. ДХ се локализират предимно в областта на главата и шията и по-рядко по тялото. Момичетата са засегнати 2 до 4 пъти по-често, както и недоносените кърмачета с тегло при раждането под 1 kg [5, 6].

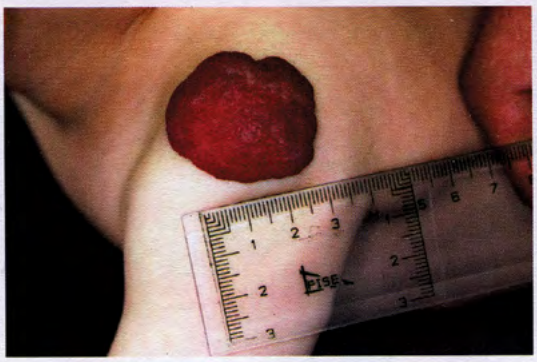
КЛАСИФИКАЦИЯ

Съществуват множество класификации на ДХ въз основа на различни критерии. Според засегнатия кожен участък ДХ могат да се разделят на:

- Фокални (локализирани) – произхождат от централен фокус /фиг. 1/.
- Сегментни (дифузни) – произхождат от голям анатомичен сегмент /фиг. 2/. При тях по-често се наблюдават усложнения, както и връзка със синдроми – PHACES, гастроинтестинални и пр. аномалии [8].
- Неопределени – те не мога да се отнесат към предходните групи [7, 8].

Друга често използвана в практика класификация на ДХ [9] ги разделя на:

- Повърхностни – в 50-60% от случаите; най-често са ярко червени плаки с лобулирана повърхност /фиг. 3/.
- Дълбоки – в 15% от случаите; меки, синьо-лилави, дълбоко разположени в дермата и подкожието нодули или плаки /фиг. 4/.
- Смесени – в 25-35% от случаите; притежават характеристики както на повърхностните, така и на дълбоките хемангиоми /фиг. 5/.



Фигура 1. ▲ *Фокален (локализиран) ДХ*

Фигура 2. ▲ *Сегментен (дифузен) ДХ*

Фигура 3. ▲ *Повърхностен ДХ*

Фигура 4. ▲ *Дълбок ДХ*

Фигура 5. ▲ *Смесен ДХ*

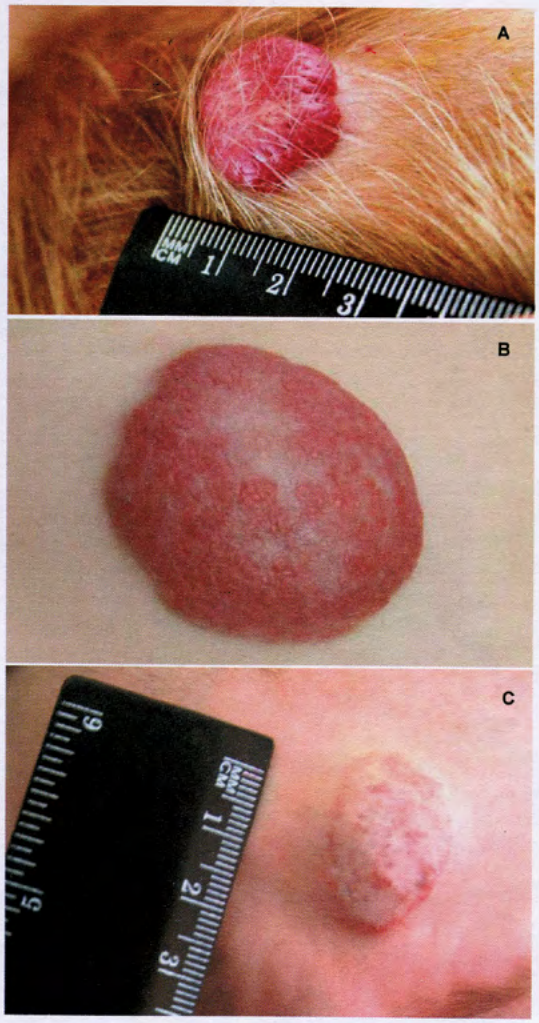
КЛИНИЧНА КАРТИНА И РАЗВИТИЕ НА ДХ

Развитието на ДХ преминава през три еволютивни фази /фиг. 6/ [10, 11]:

- Пролиферативна фаза – започва през 1-3 месец и продължава най-често до 12-18 месец: ДХ увеличават размерите си в рамките на засегнатият анатомичен сегмент /фиг. 6А/.
- Фаза на обратно развитие – започва през 2-рата година и продължава няколко години /фиг. 6Б/

Повече от 90% от ДХ регресират до края на деветата година. Цветът им се променя към сиволилаво и в центъра се появяват бели участъци, които постепенно се разширяват.

- Фаза на завършено обратно развитие – ДХ е достигнал максимална регресия /фиг. 6В/. При 30% от случаите след приключване на тази фаза остават постинволутивни промени, включващи цикатризация, хипопигментация, телеангиектазии, мастна тъкан и др.



Фигура 6. ▲ *Фази на развитие на ДХ: (А) Пролиферативна фаза; (Б) Фаза на обратно развитие; (В) Фаза на завършено обратно развитие*

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УСЛОЖНЕНИЯ ПРИ ДХ

ДХ с бавен растеж и тези, които не обхващат големи площи, особено по тялото и крайниците, обичайно не водят до усложнения. Лицевите хемангиоми обаче, в зависимост от големината си, могат да завършат фазата си на обратно развитие с неестетични остатъчни промени и поради това навременното им и адекватно лечение е изключително важно. Пери- и интраорбиталните хемангиоми могат да доведат до анизометропия, астигматизъм и дори до загуба на зрение. В тези случаи е необходимо незабавно лечение в сътрудничество с детски офталмолог [12,13]. ДХ около устата могат да затруднят приема на храна и да доведат до трайна деформация на устните, челюстите или зъбите. Назалните хемангиоми по подобен начин може да доведат до аномалии на носния скелет и нарушения във вентилацията. Силно васкуларизираните хемангиоми на ушната мида често водят до деформации на хрущяла и хипертрофия [14]. ДХ в аногениталната област имат изразена тенденция към разязвяване, което може да бъде причина за кървене, инфекция, болка и дерматит.

ЛЕЧЕНИЕ НА ДХ

Лечението на ДХ е спорен въпрос поради невъзможността да се предвиди хода на развитие на всяка отделна лезия. Изключително трудна е преценката кога да се започне лечението и какво да бъде то [15,16]. Основните индикации за лечение на ДХ включват:

1. Животозастрашаващи и нарушаващи функцията ДХ (напр. хемангиоми на черния дроб, дихателните пътища и пр.);

2. ДХ на места с висок риск от образуване на белези;

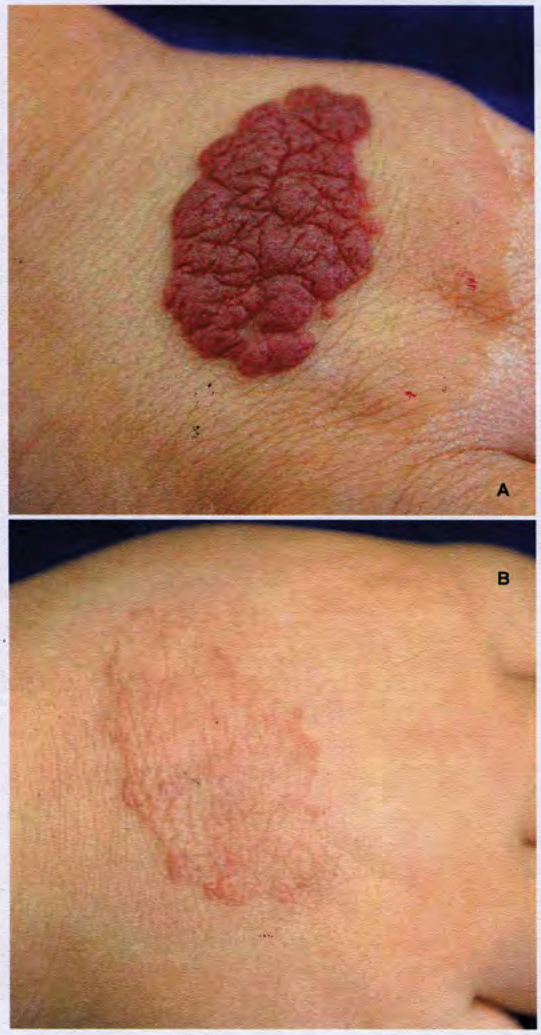
3. Обширни лицеви хемангиоми с голяма дермална компонента;

4. Малки хемангиоми в области с висок риск от нараняване (лице и ръце);

5. Улцерирали хемангиоми.

Съвременните възможности за лечение на ДХ включват: проследяване, кортикостероиди, интралезионална апликация на интерферон-α, imiquimod, vincristine, хирургия, както и прилагането на лазерно третиране.

Действието на лазерите се основава на принципа на селективната фототермолиза, който гласи, че чрез селективно въздействие върху даден специфичен хроматофор е възможно той да се унищожи без засягане на околните тъкани [17]. Таргетният хроматофор при съдовите лезии е оксихемоглобинът в еритроцитите. След абсорбцията на светлинната енергия, тя се превръща в топлинна, предизвикваща селективна фотокоагулация и тромбоза на кръвоносните съдове. Понастоящем най-често използваните системи за третиране на съдови лезии са 532-nm potassium titanyl phosphate (KTP) лазер, 755-nm alexandrite лазер и long-pulse 1064-nm neodymium-doped yttrium aluminium garnet (Nd:YAG) лазер. Използват се също и източници на пулсираща светлина (IPLs). Нашият опит показва, че дълбоко разположените участъци на ДХ може да се третират успешно с long-pulse 1064-nm Nd:YAG лазер /фиг. 7/ [18]. Този лазер има тесен спектър на безопасност и крие виоки рискове от изгаряне, пигментни нарушения и образуване на цикатрикси [19].



Фигура 7. *Лазерно лечение на ДХ: **(А)** преди началото на терапията; **(Б)** 3 месеца след 4-та процедура с Long-pulse 1064 nm Nd: YAG laser*

ЗАКЛЮЧЕНИЕ

На базата на достъпната литература и нашия собствен опит можем да заключим, че лазерната терапия е ефективен и сравнително безопасен начин за третиране на ДХ, когато е прилагана от квалифицирани медицински специалисти. Понастоящем липсват единни и унифицирани стандарти и параметри за работа с лазерните системи. Това прави трудно съпоставянето на постигнатите резултати от клиничните проучвания.

Contents

БИБЛИОГРАФИЯ

1. Masatoshi J, Tsuyoshi I, Eileen B, et al. Recent progress in studies of infantile hemangioma. Journal of Dermatology 2010; 37: 939-55.
2. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982; 69: 412-23.
3. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol 1997; 13: 375-423.
4. Frieden IJ, Haggstrom AN, Drolet BA, et al. Infantile hemangiomas: Current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas, April 79, 2005, Bethesda, Maryland, USA. Pediatr Dermatol 2005; 22(5): 383-406.
5. Bruckner AL, Frieden IJ. Infantile hemangiomas. J Am Acad Dermatol 2006 55(4): 671-82.
6. Metry D. Update on hemangiomas of infancy. Curr Opin Pediatr 2004; 16(4): 373-7.
7 Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes and their relationship to race, ethnicity and sex. Arch Dermatol 2002; 138(12): 1567-76.
8. Waner M, North PE, Scherer KA, et al. The nonrandom distribution of facial hemangiomas. Arch Dermatol 2003; 139(7): 869-75.
9. Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. Curr Probl Dermatol 1996; 26(1): 3-39.
10. Chang LC, Haggstrom AN, Drolet BA, et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics 2008; 122(2): 360-7 doi: 10.1542/peds.2007-2767
11. North PE, Mihm MCJr.Histopathological diagnosis of infantile hemangiomas and vascular malformations. Facial Plast Surg Clin North Am 2001; 9(4): 505-24.
12. Landthaler M, Hohenleutner U, Vogt T (2002) Benigne GefдЯfehl- und Neubildungen der Haut. Blackwell, Berlin Wien.
13. Lieb W, von Scheven A. Hдmangiome im Lidbereich. Ophthalmologe 2001; 98(12): 1209-23; quiz 1224-5.
14. Waner M, Suen JY. Hemangiomas and vascular malformations of the head and neck. Wiley-Liss 1999, New York.
15. Bruckner AL, Frieden IJ. Haemangiomas of infancy. J Am Acad Dermatol 2003; 48(4): 477-93; quiz 494-6.
16. Frieden IJ, Eichenfield LF, Esterly NB, et al. Guidelines of care for haemangiomas of infancy. American Academy of Dermatology Guidelines/Outcomes Committee. J Am Acad Dermatol 1997; 37(4): 631-7.
17 Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science 1983; 29: 524-7.
18. Шеф А, Кадурина М. Съдови аномалии: port wine stains и детски хемангиоми. Светлинни и лазерни въздействия като ефективен терапевтичен подход в тяхното лечение. Сп. Дерматология и венерология 2012; бр. 1: 25-35.
19. Stratigos AJ, Dover JS, Arndt KA. Laser therapy. In: Bolognia JL, Jorizzo JL, Rapini RP (eds). Dermatology. London: Mosby 2003: 2153-75.

Vascular anomalies: Port wine stains and infantile hemangiomas. Light devices as an effective therapeutic approach in their treatment

Съдови аномалии: port wine stains и детски хемангиоми. Светлинни и лазерни въздействия като ефективен терапевтичен подход в тяхното лечение

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Vascular Anomalies: Port Wine Stains and Infantile Hemangiomas. Light and Laser Devices as an Effective Therapeutic Approach in Their Treatment

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Резюме

Съдовите аномалии се разделят на две големи групи: съдови тумори и съдови малформации, като най-срещаните в ежедневната практика са детските хемангиоми и port wine stains (nevus flammeus). Детските хемангиоми са най-честите доброкачествени тумори в ранна детска възраст, които се характеризират с начална фаза на бърза пролиферация и растеж, след което следва бавно обратно развитие и възможност за намаляване на лезията. В повечето случаи те не се нуждаят от незабавна терапия, поради очакваната спонтанна регресия. Съществуват много терапевтични подходи при тяхното лечение: медикаментозна, хирургична и лазер терапия.

Port wine stains (PWSs) са най-честите съдови малформации, които обикновено са налице още при раждането. Те растат пропорционално с растежа на детето, като постепенно потъмняват на цвят и хипертрофират. Златен стандарт при лечението на пациенти с PWSs е лазерната терапия.

Настоящият обзор има за цел да направи систематизиран преглед на съвременните представи за тяхната морфология, клинична картина и лечение посредством светлинни и лазерни системи.

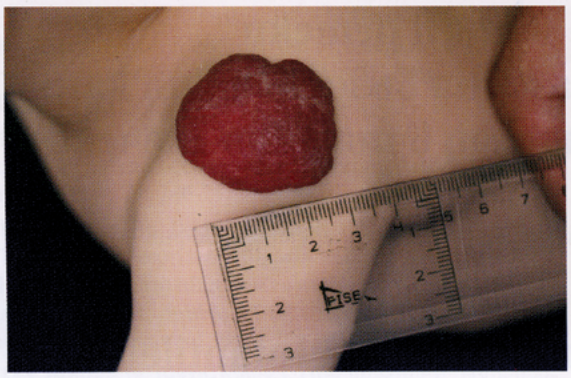
Ключови думи: съдови аномалии, детски хемангиоми, PWSs, лазерни и светлинни системи

Abstract

Vascular anomalies are divided into two major groups: vascular tumors and vascular malformations, the most common in daily practice are childhood hemangiomas and port wine stains (nevus flammeus) Infantile hemangiomas are the most common benign tumors of infancy, characterized by an initial phase of rapid proliferation and growth, followed by slow regression and the ability to reduce lesion. In most cases they do not need immediate treatment because of the expected spontaneous regresiya.There are many therapeutic approaches to their treatment: medication, surgery and laser therapy.

PWSs are the most common vascular malformations, which are usually present at birth. They grow proportionately with the growth of the child, gradually get darker in color and hypertrophy. Gold standard in treating patients with PWSs is laser therapy. This review aims to make a systematic review of current concepts of their morphology, clinical features and treatment using modern light and laser devices.

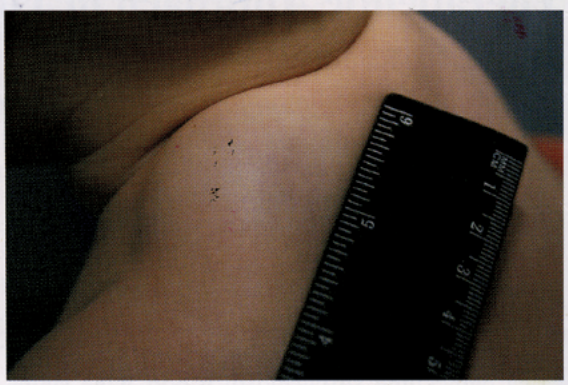
Keywords: vascular anomalities, infantile hemangiomas, PWSs, laser and light devices



Фигура 1. Фокален (локализиран) ДХ

Фигура 3. Повърхностен ДХ

Фигура 2. Сегментен (дифузен) ДХ



Фигура 4. Дълбок ДХ

Въведение

Терминът **„съдови аномалии“** включва множество състояния, които са резултат от нарушения в процесите на съдовата морфогенеза. Съдовите аномалии на аортата, белодробните съдове или вените на крайниците обикновено представляват вариации в тяхната анатомия, докато **кожните съдови аномалии** се характеризират с клетъчна хиперплазия и/или дилатация на диспластични съдове.

Различните съдови аномалии на кожата много често и неправилно се описват от клиницистите с общия термин „хемангиоми“ [1]. Според класификацията, предложена от Mulliken и Glowacki [2] през 1982 г., съдовите аномалии могат да бъдат разделени на хемангиоми и съдови малформации въз основа на биологичното им поведение и патогенеза. При последвалото преразглеждане на тази класификация от 1996 г. съдовите аномалии биват разделени на две големи групи: **съдови тумори** и **съдови малформации** [3]. Тази съвременна актуализирана класификация е одобрена от Международната асоциация за изследване на съдови аномалии (ISSVA) и дава възможност да се установи общ език сред много различни медицински специалисти, участващи понастоящем в лечението на тези състояния (табл. 1).

Детски хемангиоми

Дефиниция и епидемиология

Детските хемангиоми (ДХ) са най-честите доброкачествени тумори в кърмаческа и детска възраст, които се срещат при 10–12% от децата до една година [4]. По-малко от 20% от хемангиомите се демонстрират още при раждането, а приблизително 80–90% от тях се появяват през първите 4 седмици от живота от прекурсорна лезия като групирани телеангиектазии, еритемни или синкави макули и плаки. ДХ са разположени предимно в областта на главата и шията и по-рядко в областта на тялото. Момичетата са засегнати от 2 до 4 пъти по-често от момчетата, както и недоносените кърмачета с тегло при раждане под 1 kg [5, 6].

Класификация

Съществуват множество класификации на ДХ въз основа на различни критерии. С дидактическа цел ще спомена само двете най-широко използвани:

Според засегнатия кожен участък ДХ могат да се разделят на:

Фокални (локализирани) – произхождащи от един централен фокус (фиг. 1).

Сегментни (дифузни) – произхождащи от голям анатомичен сегмент (фиг. 2). Този подтип по-често може да доведе до усложнения, както и да е свързан със системни аномалии като синдром PHACES, гастроинтестинални и генитоуретрални аномалии [7].

Неопределени – които не могат да се класифицират като фокални или сегментни [7, 8].

Друга често използвана в практика класификация на ДХ ги разделя на:

Повърхностни – заемат до 50–60% от случаите, като най-често са еритемни (яркочервени) плаки с лобулирана повърхност (фиг. 3).

Дълбоки – заемат 15% от случаите и представляват меки, синьо-лилави, дълбоко разположени в дермата и подкожието нодули или плаки (фиг. 4).

Смесени – заемат 25–35% от случаите и притежават характеристики както на повърхностните, така и на дълбоките хемангиоми (фиг. 5) [9].

Клинична картина и развитие на ДХ

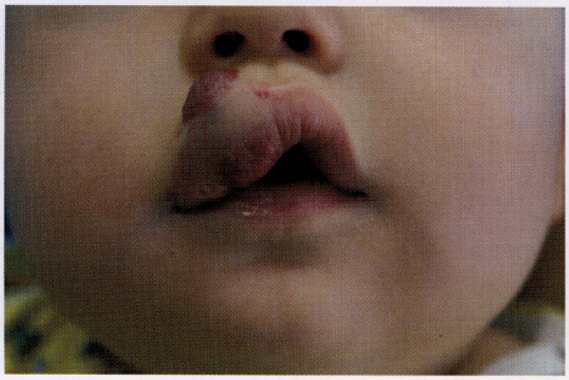
Хемангиомите в кърмаческа и детска възраст са доброкачествени пролиферации съдови тумори, които преминават последователно през три фази на развитие в хода на своята еволюция:

- **Пролиферативна фаза** – започва през 1–3 месец и продължава най-често до 12–18 месец, като ДХ увеличават размерите си в рамките

Таблица 1. Класификация на съдовите аномалии, приета от Международната асоциация за изследване на съдови аномалии (ISSVA)

Vaskular tumors	Vascular malformations
Infantile hemangiomas	Slow-flow vascular malformations
Congenital hemengiomas(RICH and NICH)	Capillary malformatiom (CM)
Tufted angioma (with or without Kasabach- Merritt syndrome)	Port-wine stain
Kaposiform hemangioendothelioma (with or without Kasabach- Merritt syndrome)	Telangiectasia
Spindle cell hemangioendothelioma	Angiokeratoma
Other, rare hemangioendotheliomas (e.g. epithelioid, composite, retiform, polymorphous, Dabska tumor lymphangioendotheliomatosis)	Cvenous malformation (VM)
Dermatological acquired vascular tumors (e.g. pyogenic granuloma, targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma)	Common sporadic VM
	Bean syndrome Famillial cutaneous and mucosal venous malformation (VMCM) Glomuvenous malformation (GVM) (glomangioma) Maffucci syndrome Lymphatic malformation (LM) Fast- flow vascular malformations Arterial malformation (AM) Arteriovenous fistula (AVF) Arteriovenous malformation (AVM) Complex- combined vascular malformations CVM, CLM, LVM, CLVM, AVM-LM, CM- AVM

C, capilary; V, venous; L, lymphatic; AV, arteriovenous; M, malformation; RICH, rapidly involuting congenital hemangioma; NICH, non- involutinga congenital hemangiom



Фигура 5. Смесен ДХ

Фигура 7 ДХ във фаза на обратно развитие

Фигура 6. ДХ в пролиферативна фаза

Фигура 8. ДХ във фаза на завършено обратно развитие

на засегнатия анатомичен сегмент (фиг. 6). Дълбоките хемангиоми се появяват по-късно и нарастват по-дълго време. В този период ДХ се състоят от деликатни лобули от малки капиляри с ендотелни клетки и перицити, разделени от тънки прегради нормална съединителна тъкан. Наблюдават се множество митози и периваскуларни мастоцити [10, 11].

- **Фаза на обратно развитие** – започва през 2-та година и продължава няколко години (фиг. 7). Повече от 90% от хемангиомите регресират до края на деветата година. Цветът на ДХ се променя към сиво-лилаво и в центъра се появяват бели участъци, които постепенно се разширяват към периферията на лезията. Хистологично се наблюдава намаляване броя на капилярите и задебеляване на базалната мембрана [10, 11].
- **Фаза на завършено обратно развитие** – когато ДХ е достигнал максимална регресия (фиг. 8). При 30% от случаите след приключване на тази фаза остават постинволутни промени, включващи цикатризация, хипопигментация, телеангиектазии, мастна тъкан и др. Хистологично в края на тази фаза ДХ се заместват от рехава фиброзна или мастна тъкан, с остатъчни „ghost" съдове [10, 11].

Усложнения при ДХ

ДХ, които нямат бърз растеж, не обхващат големи площи от кожата, особено тези по тялото и крайниците, и обикновено не водят до усложнения в хода на своето развитие. **Лицевите хемангиоми**, в зависимост от големината си, могат да завършат фазата си на обратно развитие с естетически неприемливи остатъчни промени по кожата, поради което при такива случаи е изключително важно тяхното навременно и адекватно лечение. **Пери- и интраорбиталните хемангиоми**, нарушаващи визуса и/или притискащи очната ябълка, биха могли да доведат до анизометропия, астигматизъм и в редки случаи до загуба на зрение. В тези случаи е необходимо сътрудничество с детски офталмолог и незабавна терапия [12, 13]. **ДХ около устата** могат да затруднят приема на храна и да доведат до трайна деформация на устните, челюстите или зъбите. **Назалните хемангиоми** по подобен начин могат да доведат до аномалии на носния скелет и да нарушат вентилацията през носа. Силно васкуларизираните хемангиоми

Фигура 9. PWS по хода на V2 и V3 на n.trigeminus

Фигура 10. PWS с нодуларни изменения

на ушната мида често водят до деформации и хипертрофия на хрущяла [14]. ДХ в аногениталната област имат изразена тенденция към разязвяване, което може да бъде причина за кървене, инфекция, болка и дерматит. Големите и обширни хемангиоми, със или без язви, могат да причинят нарушения в кръвообращението, да предизвикат кървене и коагулационни смущения.

В обобщение, следните хемангиоми могат да имат проблемно развитие и могат да дадат усложнения, поради което се изисква активна намеса: хемангиоми на лицето (по-специално периорбитален, периорален или на ухото), хемангиоми на устните или носа и тези в аногениталната област [14].

Port wine stain

Дефиниция и епидемиология

Port wine stains (PWS), познати още като nevus flammeus, са най-честите капилярни малформации, наблюдавани при 0,3-0,5% от всички новородени [15, 16]. Тези лезии са налице още при раждането и обикновено са разположени в

Фигура 11. PWS с хипертрофия на меките тъкани и долната устна

областта на главата и шията. Наблюдават се с еднаква честота при двата пола [15].

PWSs, засягащи главата, често могат да се наблюдават при някои редки заболявания на централната нервна система – като Sturge-Webber, а тези по единия крайник могат да бъдат част от синдрома на Klippel Trenaunay-Weber [17, 18].

Клинична картина и развитие на ДХ

PWS се демонстрират още при раждането като розови, добре ограничени лезии, локализирани или със сегментен характер, разположени най-често по хода на трите клона на тройния нерв (n. trigeminus) – офталмичен клон V1 (горен клепач и чело); максиларен клон V2 (горна устна, бузи, долен клепач) и мандибуларен клон V3 (фиг. 9).

PWSs растат пропорционално с растежа на детето, постепенно се задебеляват, потъмняват на цвят до наситено червено-лилав цвят, като по повърхността им могат да се появят единични нодули. Тези съдови малформации могат да доведат до хипертрофия на подлежащите меки тъкани и кости, особено при пациенти със синдрома на Sturge-Webber и Klippel-Trenaunay (фиг. 10–11) [19]. PWS могат да се асоциират и с други синдроми като Parkes Weber syndrome, Proteus syndrome, phakomatosis pigmentovascularis I dr.

Патология и патогенеза на PWS

Патогенезата на тези капилярни малформации е все още неясна. Няколко изследвания в тази насока са предложили хипотезата, че PWSs са резултат от увреждане на невралната инервация около дилатираните кръвоносни съдове със загуба на автономната им регулация [20, 21]. Посредством имунохистохимия е установено намален брой на нервните влакна в засегнатите участъци от кожата на пациенти с PWS [22].

Въпреки че PWSs обикновено са вродени съдови

малформации, които се появяват спорадично, през 1993 г. Pasyk и колектив [23] описват клинична форма на PWS, при която се наблюдава фамилно унаследяване на лезиите.

Основните хистопатологични промени, които се наблюдават при PWSs, са множество дилатирани капиляри в папиларната и ретикуларната дерма, чийто брой се увеличава с възрастта. Установено е, че лезиите по хода на мандибуларния клон (V1), шията и врата са разположени по-повърхностно в сравнение с лезиите по максиларния клон (V2) и крайниците [24, 25].

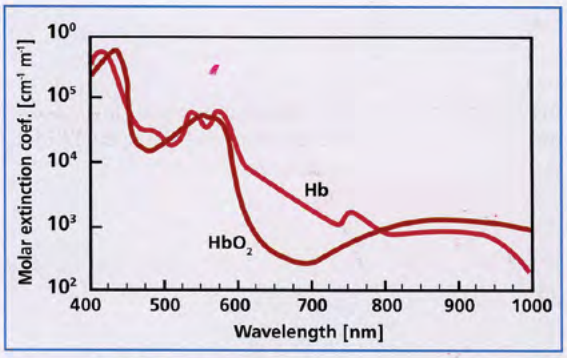
Диференциална диагноза на PWS от ДХ

Няколко основни критерии, по които клинично можем да отдиференцираме тези най-чести съдови аномалии – PWS и ДХ, са представени в таблица 2.

Светлинни и лазерни въздействия в лечението на детските хемангиоми и port wine stains

Лазерите за първи път са използвани за лечение на кожни заболявания през **1963 г. от Leon Goldman** [26]. В началото са прилагани за лечение на вродени лезии. По-късно се установило, че лазерите могат да бъдат ефективни и при терапията на придобити лезии.

Действието на лазерите и некохерентните интензивни пулсиращи източници на светлина (IPLs) се базират на **принципа на селективната фототермолиза**, описана за пръв път от **Parris и Anderson** през 1983 г. [27]. Тази теория гласи, че чрез селективно въздействие върху всеки специфичен хромофор е възможно той да се унищожи без засягане на заобикалящата го тъкан. Таргетният хромофор при съдовите лезии е **оксихемоглобинът** (HbO_2) в еритроцитите. Оксихемоглобинът има три големи пика на абсорбция при 418, 542 и 577 nm, като най-оптимално е усвояването между 577–600 nm (фиг. 12) [26].



Фигура 12. Абсорбционна крива на хемоглобина

След абсорбцията на светлинната енергия от оксихемоглобина, тя се превръща в топлинна енергия. Топлинната енергия се разпространява радиално в рамките на кръвоносните съдове, предизвиква селективна фотокоагулация, като крайният резултат е тромбоза на кръвоносните съдове. Ако продължителността на лазерния импулс е по-дълга от топлинното време на релаксация, настъпва неселективно термично увреждане на съединителната тъкан около кръвоносните съдове, което води до цикатрикси.

Понастоящем най-често използваните устройства за третиране на съдови лезии включват: 532-nm potassium titanyl phosphate (**KTP**), 595-nm pulsed dye laser (**PDL**), 755-nm **alexandrite**, 1064-nm neodymium-yttrium – aluminum-garnet (**Nd:YAG**) и различни източници на пулсираща светлина (IPL).

Port wine stains

PWSs могат да бъдат причина за значителни психологични и социални проблеми, което налага лечението им [28]. Chapas и колектив [29] доказ-

Таблица 2

Детски хемангиоми	PWS
80% се появяват между 2-ра и 5-та седмица **след раждане**	налични **още при раждането**
главата и шията, по рядко в областта на тялото	най-често в областта на лицето, по хода на клоновете на **n. trigeminus**
около 90% от ДХ **регресират** до деветата година	**не регресират** спонтанно
нарастват **само в обема на дефинирания анатомичен сегмент**	**растат пропорционално с възрастта** на детето, променят цвета си към тъмночервено-лилаво, задебеляват, могат да се появяват нодули
обикновено **няма засягане на подлежащите тъкани и кости**	често водят до **хипертрофия на подлежащите меки тъкани и кости** (Sturge-Webber, Klippel-Trenaunay)

ват, че започването на лазертерапия в ранно детство е от съществено значение за постигане на по-добър краен резултат. В противоречие с това изследване са резултатите от проучването на Van Der Horst и колектив [30] през 1998 г., при което те не установяват статистически значима разлика в крайния постигнат резултат при различните възрастови групи.

Важно е да се отбележи, че някои PWSs могат да се появят години след приключване на лечението [28]. През 1996 г. Orten и сътр. [31], в проведено от тях ретроспективно проучване при 64 пациенти, установяват, че 3% от всички пациенти имат рецидив до една година след прекратяване на лечението, а 50% от пациентите – до третата година.

Въпреки това повечето рецидиви са далеч по-малко видими в сравнение с първоначалната лезия и имат тенденция да се развиват постепенно.

Pulsed Dye Laser (PDL) е средство на избор при лечение на пациенти с PWSs, независимо от възрастта и локализацията на лезиите, поради документирана висока ефикасност и безопасност при този лазер [32]. Ефективните параметри включват: дължина на вълната 585–600 nm, енергия 6–15 J/cm^2 продължителност на пулса от 0,45–1,5 ms [28]. Хистологичните промени, които се наблюдават след третиране с PDL, включват: интактен епидермис и кръвоносни съдове в дермата, изпълнени с аглутинирани еритроцити, фибриноген и тромби. Клинично се наблюдава временна пурпура, която преминава за 7–14 дни.

Cantatore и съавт. [28] потвърждават възможността за използване на PDL при лечение на деца, поради значително ниския риск от цикатризация и перманентни пигментни нарушения. Лечението в тази ранна възраст е значително успешно поради по-тънката кожа на кърмачетата и повърхностно разположените кръвоносни съдове [33].

Важен фактор, определящ степента на повлияване на PWS при лазертерапия, е тяхната анатомична локализация [34]. До този извод стигат Renfro и Geronemus [35] след провеждане на ретроспективно проучване върху 259 пациенти и анализиране на постигнатите крайни резултати, разделяйки ги според анатомичната локализация на лезиите. Авторите заключават, че лезии в областта на главата и шията реагират на лечението с PDL по-добре от лезии по тялото и крайниците.

През 1998 г. Nguyen и съавт. [36] изследват степента на повлияване на PWSs в зависимост от възрастта на пациента, броя проведени процедури, размера и локализацията на лезията. В своето проучване те установяват, че най-важният фактор, определящ степента на повлияване на PWSs при лазертерапия, е локализацията на лезиите, следвана от големината и възрастта на пациентите. Според техните наблюдения най-добри резултати могат да се постигнат при пациенти под 1 година, които имат малки PWS под 20 cm^2, разположени върху костни области, като челото. Максимално изсветляване на лезиите се наблюдавало при първите 5 процедури, независимо от възрастта, размера и локализацията на лезията. При започване на лечение тези фактори могат да служат като прогностични маркери за очакваната степен на повлияване при конкретната лезия [36].

Mihm и сътр. [37] сравняват ефикасността от комбинираното лечение с PDL и локален imiquimod и монотерапията с PDL. Те установяват, че при локално приложение на imiquimod на лезиите – веднъж дневно, в продължение на 1 месец, след терапия с PDL има по-добър резултат от монотерапията със същия лазер. През 2008 г. Phung, Mihm и колеги [38] изследват in vivo ефективността от комбинирано използване на PDL и локален инхибитор на ангиогенезата, гаратусin. Авторите заключават, че формирането на нови съдове и реперфузията значително намалява, ако се прилага гаратусin локално след процедура с PDL.

При лечение с PDL само 20% от всички PWSs достигат до пълно изсветляване [39]. Съществуват няколко обяснения за това, защо PDL не може да коагулира всички ектатични капиляри в рамките на PWS. Те включват [40]:

- Недостатъчна дълбочина на проникване на лазерната светлина; дълбоко разположените в кожата капиляри не могат да се достигнат от PDL светлина, тъй като тя прониква до 1 mm в кожата.
- Недостатъчен обем на кръвта, следователно на таргетния хромофор хемоглобин в съдове с диаметър по-малък от 50 μm.
- Неадекватна енергия, която не позволява трайно да се увреди стената на кръвоносните съдове.

Резистентни на терапия с PDL, дълбоко разположените и хипертрофични PWS могат успешно да се третират с дълговълнови лазери като pulsed Nd:YAG laser, potassium titanyl phosphate laser (KTP) и IPL – системи, които позволяват по-дълбоко проникване в кожата [41].

Yang и сътр. [42] в своето проспективно проучване, проведено през 2005 г. върху пациенти, третирани **с Nd:YAG лазер**, доказват, че този вид лазер е по-ефикасен при лечение на нодуларни, хипертрофични и PDL резистентни PWS.

Причината за това е в по-добрата проникваща способност на лъчите, което позволява да се достигнат дълбоко разположените кръвоносни съдове.

При дължина на вълната 1064 nm oxyhemoglobin има минимална абсорбция на енергия, което значително увеличава риска от увреждане на околната тъкан, последвано от цикатризация и хиперпигментация [43]. Това налага лечението на PWSs с long-pulsed 1064 nm **Nd:YAG** лазер да се извършва от квалифицирани специалисти.

Проучване на Tanghetti и колектив [44] изследва ефикасността от последователното приложение на **PDL/Nd:YAG** при пациенти с PWS, резистентни на PDL. Те наблюдават подобрение в третираните лезии и прилагат значително по-ниски стойности на енергия от прилаганите при монотерапия с PDL или ND:YAG, което значително редуцира риска от нежелани реакции.

- **KTP (potassium titanyl phosphate) лазера с дължина на вълната 532 nm също може да се използва успешно за третиране на PDL резистентни PWS. Това доказват Chowdhury и сътр. [45] при изследване на 30 пациенти, резистентни на лечение с PDL. Те установяват значително изсветляване на лезиите и висок толеранс от страна на пациентите, поради по-малкия дискомфорт и пурпура след процедурите. Проучване на Lorenz и колектив [46] през 2003 г. сравнява ефикасността на KTP и PDL при третиране на 43 пациенти с PWS и заключава, че поради по-малкия риск от изгаряне, цикатризация и пигментни нарушения при PDL, той е предпочитано средство на избор.**

Източниците на интензивна пулсираща светлина (IPL) произвеждат некохерентни светлинни лъчи с дължини на вълните от 500 до 1200 nm. За лечение на съдови лезии се използват лъчи с дължина: 515, 550, 570, 590 nm. Това не са лазерни устройства, но работят на подобни принципи и могат да се използват самостоятелно или съвместно за лечение на PWS, чиито дълбоки компоненти не могат да се достигнат от PDL. Uzdemir и колектив [47] съобщават за умерено подобрение (50%–75%) на PWS лезиите при 47% от пациентите, които са били лекувани с IPL. Съществуват клинични доказателства в подкрепа на това проучване, показващи, че 50% от PDL-резистентните PWS могат да изсветлеят до 50% при последващо лечение с IPL [48]. При сравнение на ефективността между PDL и IPL в рандомизирано клинично проучване се доказа по-високата ефикасност и по-добра толерантност от пациентите на PDL [49].

Фотодинамичната терапия (PDT), електрокоагулацията, криохирургията и козметичният грим са други алтернативни възможности за лечение на PWS.

В таблица 3 [50] са представени детайлно видовете лезии при PWS и подходящите лазерни и светли устройства за тяхното лечение.

Детски хемангиоми

Понастоящем подходът при лечението на детски хемангиоми остава изключително спорен въпрос, поради невъзможността да се предвиди еволюционният ход на развитие на всяка конкретна лезия. Съществуват хемангиоми, които претърпяват пълно обратно развитие без необходимост от терапия, както и хемангиоми, които започват да растат екстремно и водят до животозастрашаващи усложнения. Това прави изключително трудна преценката на специалистите кога да се започне активно лечение [51]. Някои школи препоръчват агресивен подход в лечението на детските хемангиоми с оглед да се намали вероятността от развитие на потенциално застрашаващи усложнения, докато други школи съветват да се приеме „активна ненамеса“ (wait-and-see approach) – активно проследяване и терапевтична намеса само при необходимост [51].

Консенсусът от 1997 г. за лечение на детски хемангиоми, приет от комитета на Американската академия по дерматология [52], посочва основните цели при лечението на детските хемангиоми:

Таблица 3. Видове лазери, използвани за третиране на PWS

Видове лезии при PWS	Подходящ лазер
Светло- до тъмнорозови макули, с фини кръвоносни съдове 50–80 μm	PDL, KTP, IPL
Ясно ограничени червени лезии, с единични видими с невъоръжено око кръвоносни съдове 80–120 μm	PDL (long pulse), KTP, IPL
Тъмночервени лезии, с множество ектатични съдове 120–150 μm	PDL (long pulse), KTP, IPL
Големи плътни тъмнолилави лезии, със силно дилатирани кръвоносни съдове > 150 μm	IPL, Nd: YAG (да се избягва периорбиталната зона)

1. Предотвратяване на усложнения, застрашаващи живота на пациента или функцията на различни органи;
2. Предотвратяване образуването на обезобразяващи цикатрикси след приключване на фазата на обратно развитие;
3. Намаляване на психосоциалния стрес за пациента и семейството му;
4. Избягване на агресивни процедури с висок риск от образуване на белези при лезии, които биха претърпели обратно развитие без необходимост от терапия;
5. Предотвратяване или лечение на разязвени хемангиоми с цел понижаване на риска от инфекции, образуване на белези и болка.

Основните индикации за лечение на детски хемангиоми, публикувани в *Journal of the American Academy of Dermatology*, включват:

1. Животозастрашаващи и функционално увреждащи хемангиоми (напр. хемангиоми на черния дроб, дихателните пътища и др.);
2. Хемангиоми на места с висок риск от образуване на трайни белези;
3. Обширни лицеви хемангиоми с голяма дермална компонента;
4. Малки хемангиоми в области, изложени на висок риск от нараняване (лице и ръце);
5. Улцерирани хемангиоми.

Според консенсуса от 1997 г. за лечение на детски хемангиоми, приет от комитета на Американската академия по дерматология, [52] видът на препоръчваното лечение при детските хемангиоми се определя от:

1. Анатомичната локализация на лезията;
2. Дълбочина на разположение на лезията в кожата;
3. Размер на лезията;
4. Текущата фаза на развитие, в която се намира лезията (пролиферация или инволюция);
5. Наличие на функционални нарушения.

Съвременните възможности за лечение на детските хемангиоми включват: активно проследяване на лезиите, кортикостероиди, интралезионална апликация на interferon alfa, imiquimod, vincristine, хирургия, както и прилагането на лазерни системи.

Употребата на лазери се очертава като една от съвременните и перспективни възможности на лечение на ДХ в последните няколко години. Те се използват основно за третиране на малки, повърхностно разположени лезии, неразязвени хемангими и резидуални телеангиектазии [51]. Използват се различни видове съдови лазери: Pulsed dye laser (PDL), kalium-titanyl-phosphat (KTP-532 nm), alehandrite laser (755 nm), диоден лазер (800-900 nm) и neodymium: yttrium – aluminium-garnet laser (Nd: YAG-1064 nm).

Фигура 13. ДХ преди лечение

Фигура 14. 3 месеца след 4-ата процедура с Long-pulse 1064 nm Nd: YAG laser

Batta и колектив [53] провеждат първото проспективно и рандоминизирано проучване при лечение с **PDL** на 121 деца с неулцерирали хемангиоми. Те стигат до извода, че липсва значима статистическа полза от започване на ранната терапия с PDL, която крие риск от атрофия и хипопигментация, в сравнение с резултати от подхода „wait-and-see“

През 1993 г. Ashinoff и Geronemus [54] изследват дали лечението с PDL може да предотврати растежа на хемангиомите в дълбочина и установяват, че въпреки доброто повлияване на повърхностните участъци на хемангиомите от лечение с PDL, дълбоките компоненти на лезиите продължават да нарастват.

Лечението с PDL лазери не е особено ефективно при дълбоки и комбинирани хемангиоми [51], поради невъзможността на лазерните лъчи да проникнат по-дълбоко от 1,2 mm в кожата. Дълбоко разположените участъци на детските хемангиоми биха могли успешно да се третират с **long-pulsed 1064 nm Nd:YAG лазер** (фиг. 13 и фиг. 14). Този лазер е в състояние да предизвика коагулация на дълбочина 5–6 mm, поради което

може да се използва за лечение на дълбоко разположени съдове с голям диаметър. Nd:YAG лазерът има тесен спектър на безопасност и крие високи рискове от изгаряния, пигментни нарушения и образуване на белези [41].

KTP лазерите, с дължина на вълната 532 nm, са друга възможна опция за третиране на дълбоки съдови лезии. KTP лазерът е всъщност вид Nd:YAG лазер, при който лъчът с дължина на вълната 1064 nm преминава през KTP кристал и се модифицира. Абсорбцията на модифицирания лъч с дължина на вълната 532 nm е изключително висока от хемоглобина, което прави този вид лазер изключително ефективен при лечение на хемангиоми. Achauer и сътр. [55] в свое проучване от 1998 г. потвърждават доброто повлияване на дълбоките хемангиоми при лечение с KTP Този извод се потвърждава и от проучване на Burstein и колектив [56], проведено върху 400 пациенти, при които е регистрано >75% редукция в размера, диаметъра и дълбочината на третираните съдови лезии.

Заключение

От прегледа на достъпните литературни източници става ясно, че лазерната терапия като цяло е безопасен и ефективен начин за третиране на PWSs и детски хемангиоми, когато е прилагана от квалифицирани медицински специалисти.

При направения научен обзор прави впечатление липсата на единни и унифицирани стандарти и параметри за работа с лазерните системи. Това прави трудно съпоставими постигнатите резултати от проведените до момента клинични изследвания. С оглед на гореизложеното е уместно в близко бъдеще да се проведат мултицентрови изследвания, имащи за цел изготвянето на единен консенсус за лечение на съдовите аномалии.

Книгопис

1. Masatoshi JINNIN, Tsuyoshi ISHIHARA, Eileen BOYE, Bjorn R. OLSEN. Recent progress in studies of infantile hemangioma. Journal of Dermatology 2010; 37· 939–955_ 2010.

2. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982; 69· 412–423.

3. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol 1997; 13: 375.

4. Frieden IJ, Haggstrom AN, Drolet BA, et al. Infantile hemangiomas: Current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas, April 7–9, 2005, Bethesda, Maryland, USA. Pediatr Dermatol 2005; 22: 383.

5. Bruckner AL, Frieden IJ (2006) Infantile hemangiomas. J Am Acad Dermatol 55: 671–682.

6. Metry D. Update on hemangiomas of infancy. Curr Opin Pediatr 2004; 16: 373.

7. Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy· clinical characteristics, morphologic subtypes and their relationship to race, ethnicity and sex. Arch Dermatol 2002; 138: 1567

8. Waner M, North PE, Scherer KA, Frieden IJ, Waner A, Mihm MC Jr. The nonrandom distribution of facial hemangiomas. Arch Dermatol 2003; 139· 869.

9. Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. Curr ProblDermatol 1995; 7· 69.

10. Chang LC, Haggstrom AN, Drolet BA, et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics 2008; 122: 360.

11. North PE, Mihm MCJr.Histopathological diagnosis of infantile hemangiomas and vascular malformations. Facial Plast Surg Clin North Am 2001, 9(4): 505.

12. Landthaler M, Hohenleutner U, Vogt T (2002) Benigne GefgЯfehl- und Neubildungen der Haut. Blackwell, Berlin Wien.

13. Lieb W, v.Scheven A (2001) Hgmangiome im Lidbereich. Ophthalmologe 98: 1209–1225.

14. Lieb W, v.Scheven A (2001) Hgmangiome im Lidbereich. Ophthalmologe 98: 1209–1225.

15. Rosen S, Geer DE, Noe JM. The nature and evolution of port wine stains: A computer-assisted study. J Invest Dermatol. 1980;74(3):154 – 7

16. Haedersdal M, Efsen J, Gniadecka M, Fogh H, Keiding J, Wulf HC. Changes in skin redness, pigmentation, echostructure, thickness, and surface contour after 1 pulsed dye laser treatment of port-wine stains in children. Arch Dermatol. 1998; 134(2):175 – 81.].

17 Enjolras O, Riche MC, Merland JJ. Facial port-wine stains and Sturge-Weber syndrome. Pediatrics. 1985;76(1):48 – 51.

18. Maari C, Frieden IJ. Klippel-Trenaunay syndrome: The importance of ' geographic stains ' in identifying lymphatic disease and risk of complications. J Am Acad Dermatol. 2004, 51(3):391 – 8.

19. Klapman MH, Yao JF Thickening and nodules in portwine stains. J Am Acad Dermatol 2001, 44: 300.

20. Smoller BR, Rosen S. Port-wine stains. A disease of altered neural modulation of blood vessels? Arch Dermatol 1986; 122: 177

21. Rydh M, Malm M, Jernbeck J, Dalsgaard CJ. Ectatic blood vessels in port-wine stains lack innervation: possible role in pathogenesis. Plast Reconstr Surg 1991, 87· 419.

22. Selim MM, Kelly KM, Nelson JS, Wendelschafer-Crabb G, Kennedy WR, Zelickson BD. Confocal microscopy study of nerves and blood vessels in untreated and treated portwine stains: preliminary observations. Dermatol Surg 2004; 30: 892.

23. Pasyk KA, Wlodarczyk SR, Jakobczak MM, Kurek M, Aughton DJ. Familial medial telangiectatic nevus: variant of nevus flammeus-portwine stain. Plast Reconstr Surg 1993; 91. 1032.

24. Barsky SH, Rosen S, Geer DE, Noe JM. The nature and evolution of PWSs: a computer assisted study. *J Invest Dermatol* 1980; 74: 154– 7.

25. Eubanks LE, McBurney EI. Videomicroscopy of port-wine stains: correlation of location and depth of lesion. J Am Acad Dermatol 2001, 44. 948.

26. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology· four decades of progress. J Am Acad Dermatol 2003;49:1-31.

27. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science. 1983 Apr 29;220(4596):524-7.

28. Cantatore JL, Kriegel DA. Laser surgery· an approach to the pediatric patient. J.

29. 29 Chapas AM, Eickhorst K, Geronemus RG. Efficacy of early treatment of facial port wine stains in newborns: a review of 49 cases. Lasers Surg Med 2007; 39(7): 563.

30. van der Horst CM, Koster PH, de Borgie CA, Bossuyt PM, van Gemert MJ. Effect of the timing of treatment of port-wine stains with the flash-lamp-pumped pulsed-dye laser. N Engl J Med 1998;338:1028-33.

31. Orten SS, Waner M, Flock S, Roberson PK, Kincannon J. Portwine stains: an assessment of 5 years of treatment. Arch Otolaryngol Head Neck Surg 1996;122:1174-9.

32. Smit JM, Bauland CG, Wijnberg DS, Spauwen PH. Pulsed dye laser treatment, a review of indications and outcome based on published trials. Br J Plast Surg 2005;58:981-7.

33. Mariwalla K, Dover JS. The use of lasers in the pediatric population. Skin Therapy Lett 2005;10:7-9.

34. Stier MF, Glick SA, Hirsch RJ Laser treatment of pediatric vascular lesions: Port wine stains and hemangiomas. J Am Acad Dermatol. 2008 Feb;58(2):261-85.

35. Renfro L, Geronemus RG. Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. Arch Dermatol 1993;129·182-8.

36. Nguyen CM, Yohn JJ, Huff C, Weston WL, Morelli JG. Facial port wine stains in childhood: prediction of the rate of improvement as a function of the age of the patient, size and location of the port wine stain and the number of treatments with the pulsed dye (585 nm) laser. Br J Dermatol 1998; 138: 821-5.

37. Chang CJ, Hsiao YC, Mihm MC Jr, Nelson JS. Pilot study examining the combined use of pulsed dye laser and topical Imiquimod versus laser alone for treatment of port wine stain birthmarks. Lasers Surg Med 2008; 40(9): 605.

38. Phung TL, Oble DA, Jia W, Benjamin LE, Mihm MC Jr, Nelson JS. Can the wound healing response of human skin be modulated after laser treatment and the effects of exposure extended? Implications on the combined use of the pulsed dye laser and a topical angiogenesis inhibitor for treatment of port wine stain birthmarks. Lasers Surg Med 2008; 40(1): 1–5.

39. Lanigan SW Port-wine stains unresponsive to pulsed dye laser: explanations and solutions. Br J Dermatol 1998; 139· 173.

40. Jasim ZF, Handley JM. Treatment of pulsed dye laser-resistant port wine stain birthmarks. J Am Acad Dermatol 2007; 57· 677-82.

41. Stratigos AJ, Dover JS, Arndt KA. Laser therapy. In: Bolognia JL, Jorizzo JL, Rapini RP, senior editors. Horn TD, Mascaro JM, Saurat JH, Mancini AJ, Salasche SJ, Stingl G, editors. Dermatology. London: Mosby; 2003. p. 2153-75.

42. Yang MU, Yaroslavsky AN, Farinelli WA, Flotte TJ, Rius-Diaz F, Tsao SS, *et al*. Long-pulsed neodymium: Yttrium aluminum-garnet laser treatment for port-wine stains. J Am Acad Dermatol 2005;52:480-90.

43. Willey A, Anderson RR, Azpiazu JL, Bakus AD, Barlow RJ, Dover JS, et al. Complications of laser dermatologic surgery. Lasers Surg Med 2006;38:1-15.

44. Tanghetti EA, Sherr E, Sierra R, Mirkov M. Sequential 595 nm, 1064 nm laser treatment for blebbed portwine stains and leg veins. Lasers Surg Med 2005;36:74.

45. Chowdhury MM, Harris S, Lanigan SW Potassium titanyl phosphate laser treatment of resistant port-wine stains Br J Dermatol. 2001 Apr;144(4):814-7.

46. Lorenz S, Scherer K, Wimmershoff MB, Landthaler M, Hohenleutner U. Variable pulse frequency-doubled Nd:YAG laser versus flashlamp-pumped pulsed dye laser in the treatment of port wine stains. Acta Derm Venereol. 2003;83(3):210-3.

47. Uzdemir M, Engin B, Mevlitoluı I. Treatment of facial port-wine stains with intense pulsed light: a prospective study. J Cosmet Dermatol 2008; 7:127-31.

48. Bjerring P, Christiansen K, Troilius A. Intense pulsed light source for the treatment of dye laser resistant port wine stains. J Cosmet Laser Ther 2003;5:7-13.

49. Faurschou A, Togsverd-Bo K, Zachariae C, Haedersdal M. Pulsed dye laser vs. intense pulsed light for port-wine stains: a randomized side-by-side trial with blinded response evaluation. Br J Dermatol 2009; 160(2):359.

50. Adamic M, Troilius A, Adatto M, Drosner M, Dahmane R. Vascular lasers and IPLS: Guidelines for care from the European Society for Laser Dermatology. J Cosmet Laser Ther 2007; 9:113-24.

51. Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003;48:477-93.

52. Frieden IJ, Eichenfield LF, Esterly NB, Geronemus R, Mallory SB. Guidelines of care for hemangiomas of infancy· American Academy of Dermatology guidelines/outcomes committee. J Am Acad Dermatol 1997; 37:631-7.

53. Batta K, Goodyear HM, Moss C, Williams HC, Hiller L, Waters R. Randomized controlled study of early pulsed dye laser treatment of uncomplicated childhood hemangiomas: results of a 1-year analysis. Lancet 2002;360:521-7.

54. Ashinoff R, Geronemus RG. Failure of the flashlamp-pumped pulsed dye laser to prevent progression to deep hemangioma. Pediatr Dermatol 1993;10:77-80.

55. Achauer BM, Celikoz B, VanderKam VM. Intralesional bare fiber laser treatment of hemangioma of infancy. Plast Reconstr Surg 1998;101.1212-7.

56. Burstein FD, Williams JK, Schwentker AR, Nahai F Intralesional laser therapy treatment for hemangiomas: technical evolution. J Craniofac Surg 2006;17·756-60.